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(54) **REGULATORY CONSTRUCTS COMPRISING INTRON 3 OF PROSTATE SPECIFIC MEMBRANE ANTIGEN GENE**

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Jan. 25, 2000 (AU) PQ5268

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A61K 48/00 (2006.01)
C12N 15/00 (2006.01)
C12N 15/86 (2006.01)
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C07H 21/04 (2006.01)

(52) **U.S. Cl.** ..... **435/456**; 435/69.1; 435/70.1; 435/70.3; 435/455; 435/320.1; 514/44 R; 536/23.1; 536/24.1

(58) **Field of Classification Search** ..... None
See application file for complete search history.

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(57) **ABSTRACT**

The invention provides a recombinant vector comprising an ovine adenovirus genome and a sequence encoding a heterologous polypeptide, wherein the sequence encoding the heterologous polypeptide is inserted between E4 and E3 transcription units of the ovine adenovirus genome.

14 Claims, 16 Drawing Sheets

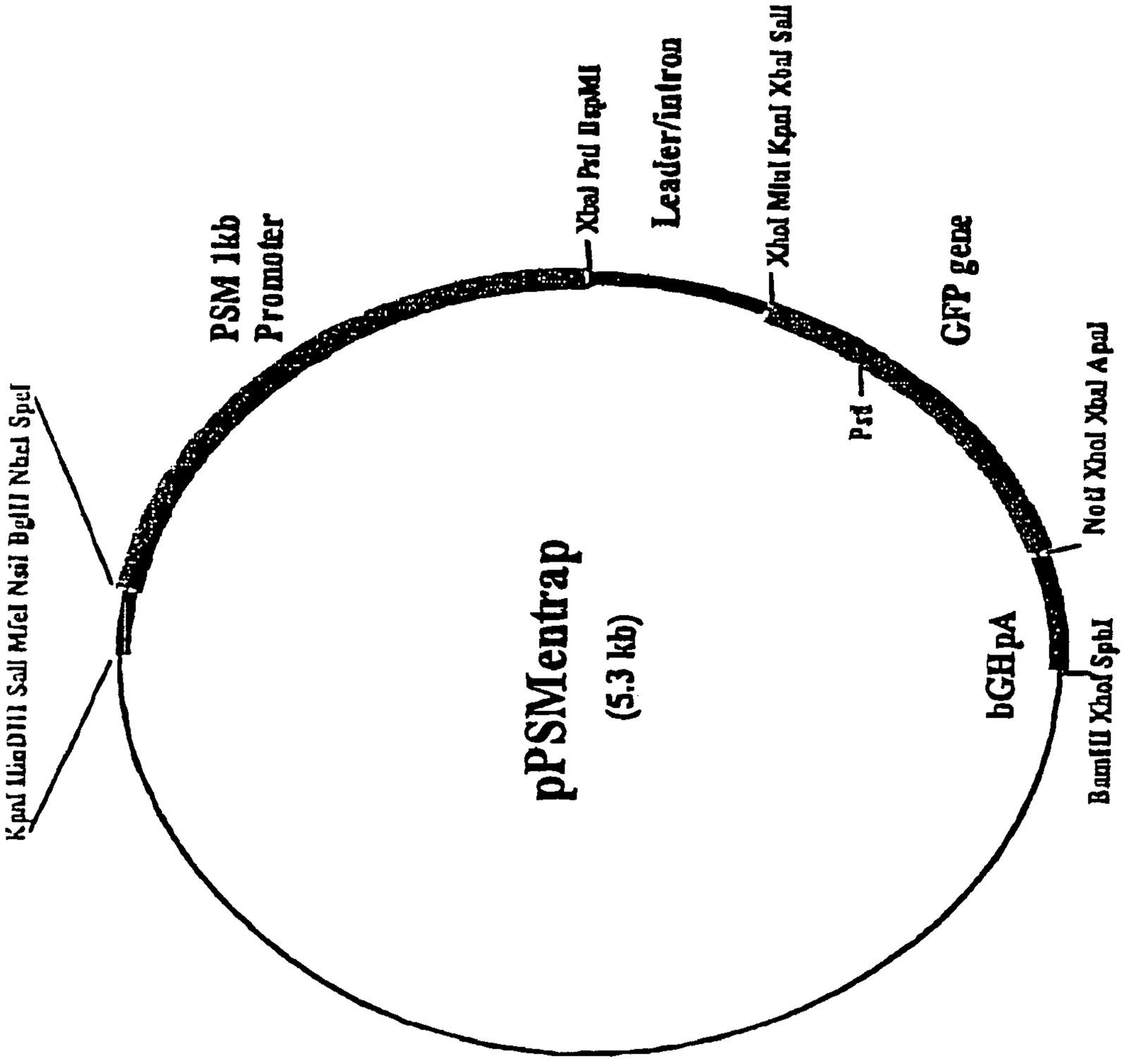

pPSMentrap
(5.3 kb)
PSM 1kb
Promoter
XbaI PstI BspMII
Leader/intron
XhoI MluI KpnI XbaI
Prd
GFP gene
NotI XhoI XbaI ApaI
bGHpA
BamHII XhoI SphI
KpnI HindIII SalI MfeI NaiI BglII NheI SpeI

Figure 1

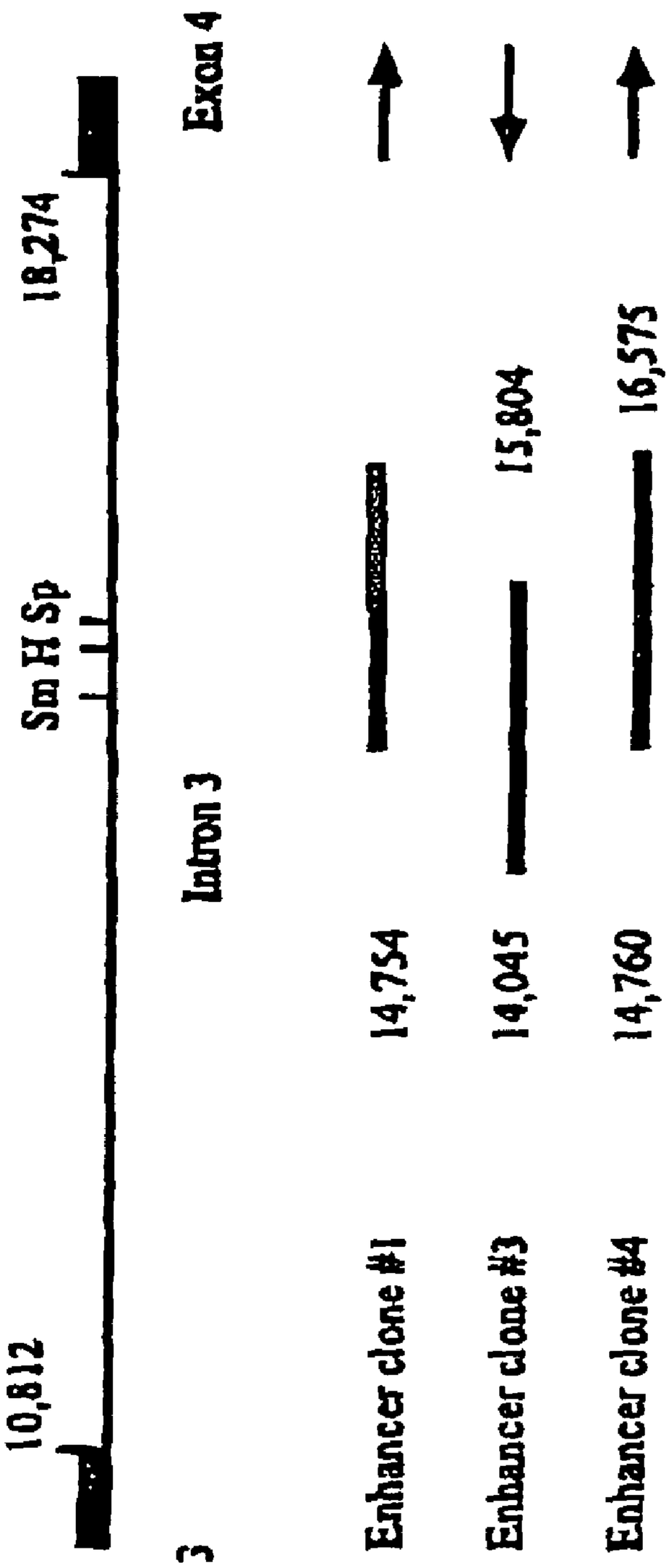

Exon 4
18,274
Sm H Sp
Intron 3
14,754
14,045
15,804
14,760
16,575
10,812
Exon 3
Enhancer clone #1
Enhancer clone #3
Enhancer clone #4

Figure 2

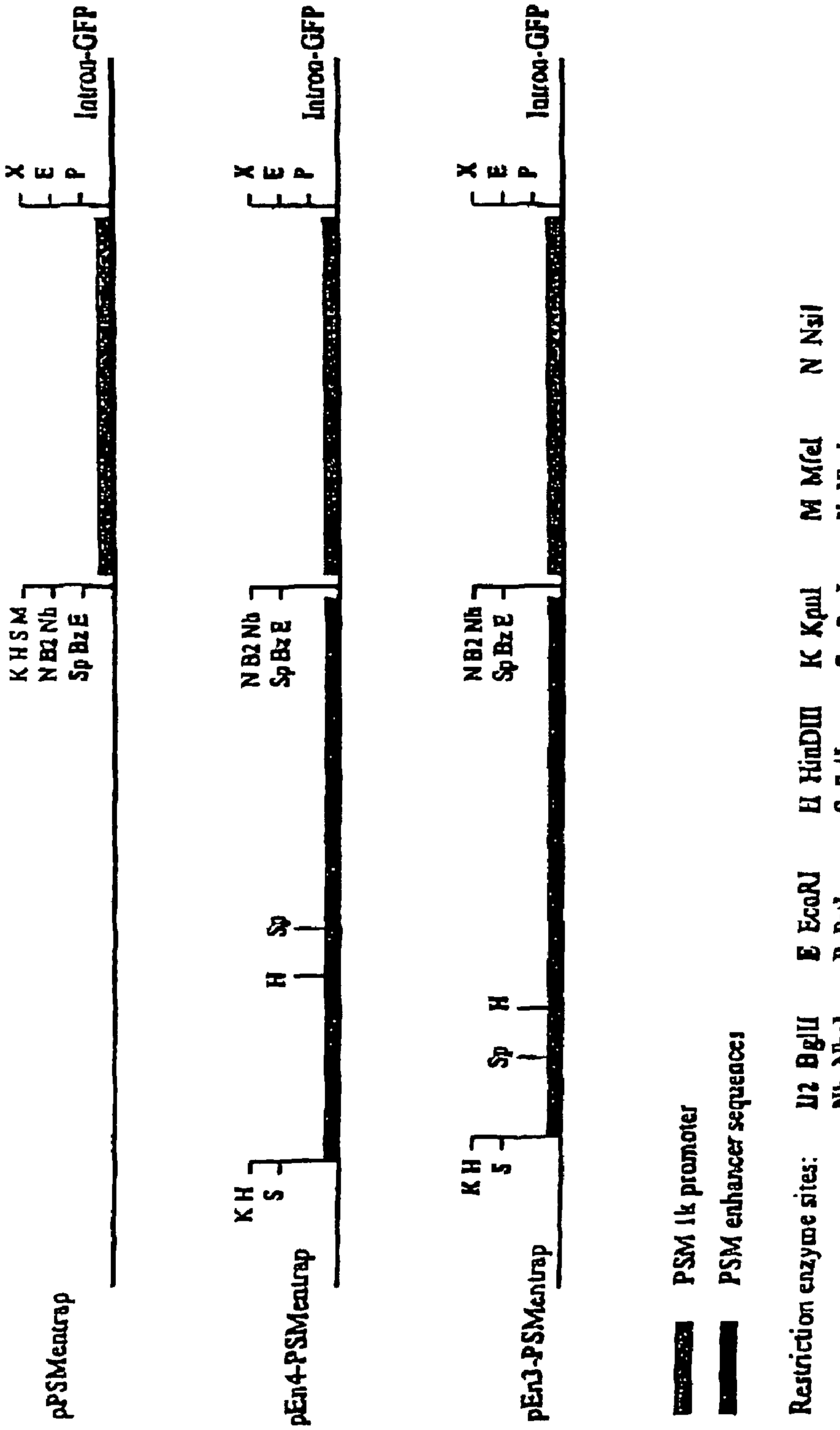

pPSMenutap
pEn4-PSMenutap
pEn3-PSMenutap
Intron-GFP
K H S M
N B2 Nb
Sp Bz E
K H
S
Sp
H
N B2 Nb
Sp Bz E
PSM 1k promoter
PSM enhancer sequences
Restriction enzyme sites:
B2 BglII
Nb NheI
E EcoRI
P PstI
H HindIII
S SalI
K KpnI
Sp SpeI
M MfeI
X XbaI
N NsiI

Figure 3

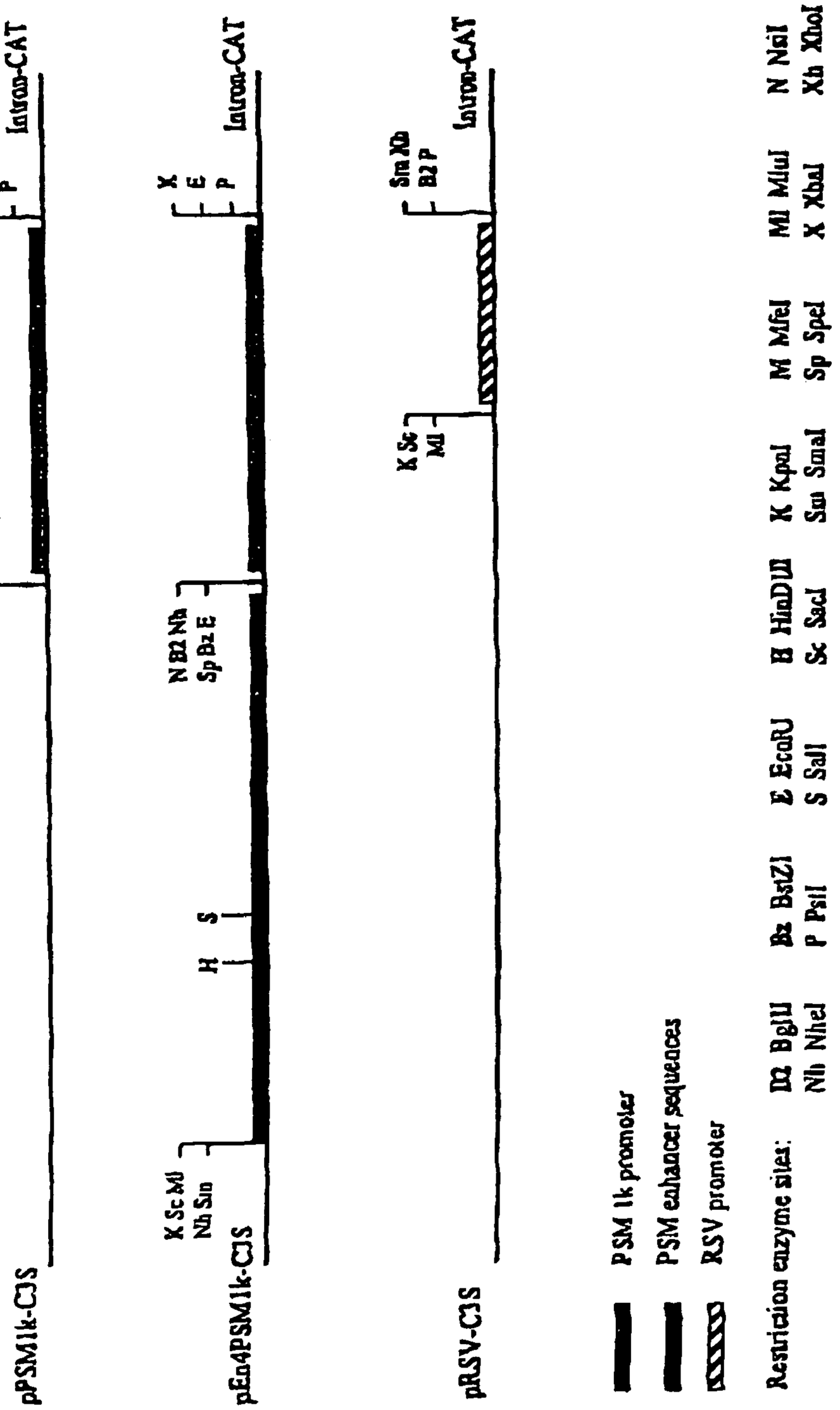

pPSM1k-CIS
pEn4PSM1k-CIS
pRSV-CIS
Intron-CAT
PSM 1k promoter
PSM enhancer sequences
RSV promoter
Restriction enzyme sites:
Bx BstZI
P PstI
E EcoRI
S SalI
H HindIII
Sc SacI
K KpnI
Sm SmaI
M MfeI
Sp SpeI
Ml MluI
Xb XbaI
N NotI
Xh XhoI
Bg BglII
Nh NheI

Figure 4

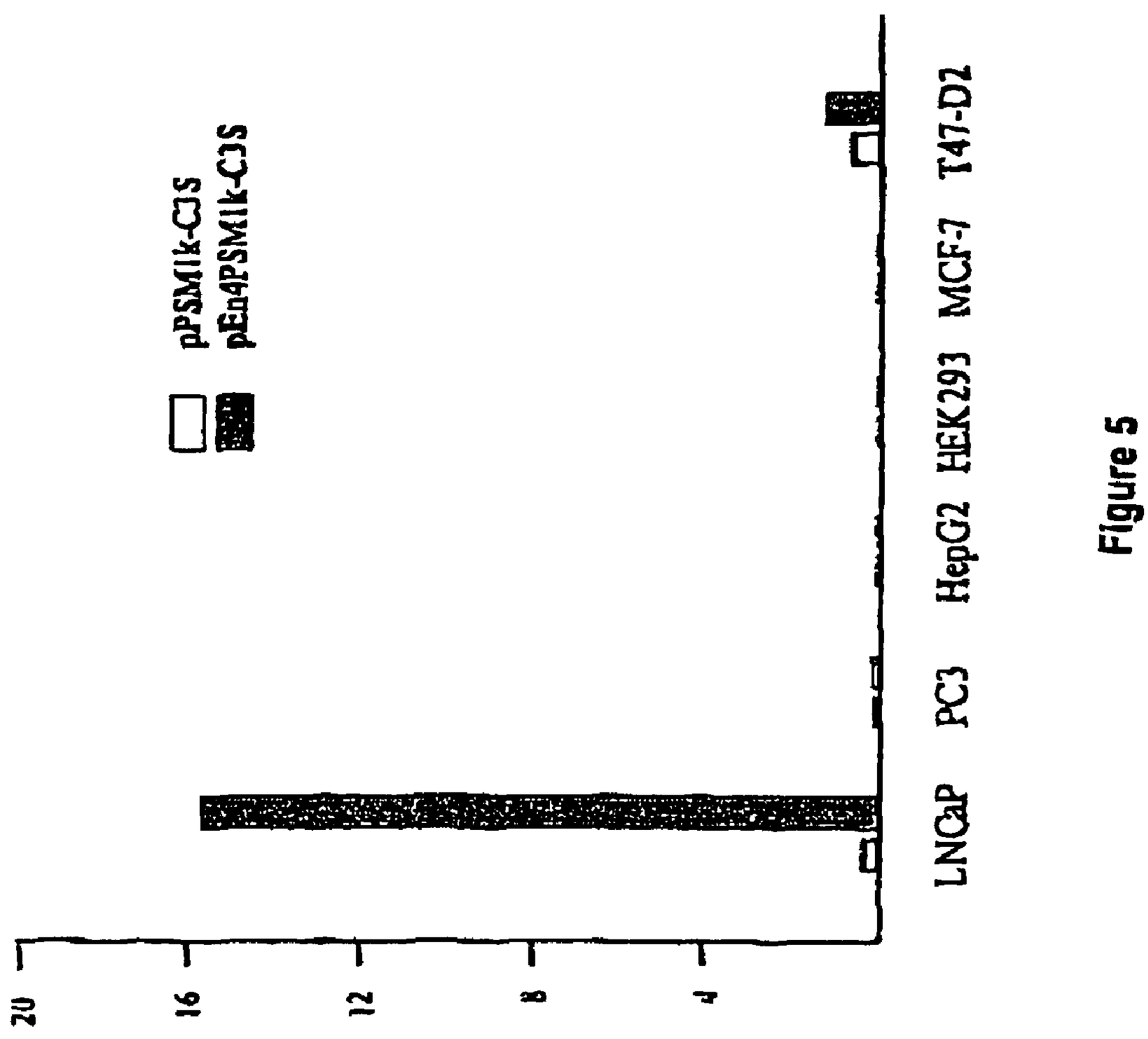

pSM1k-C3S
pEn4PSM1k-C3S
Activity relative to RSV promoter (%)
20
16
12
8
4
LNCaP
PC3
HepG2
HEK293
MCF-7
T47-D2

Figure 5

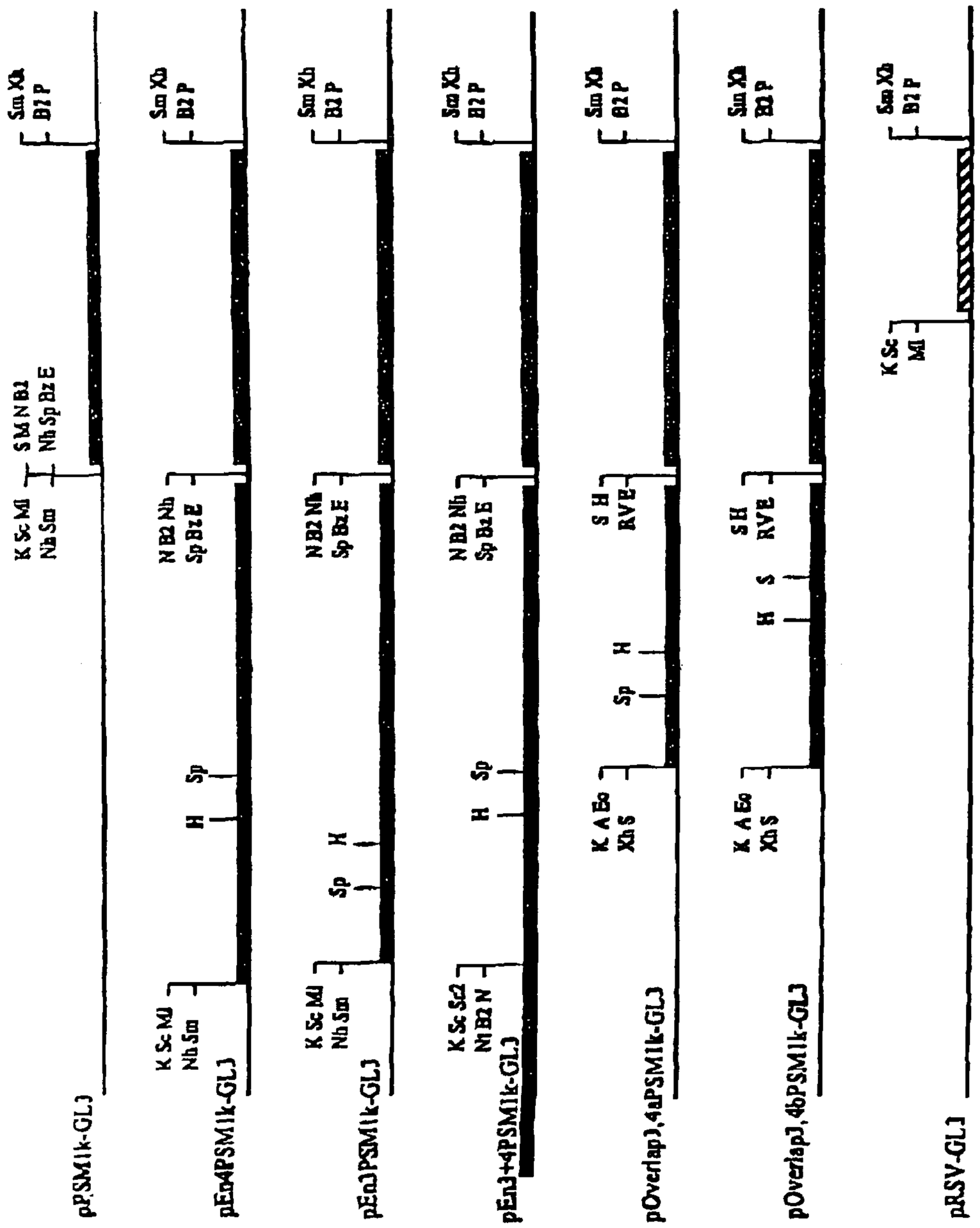

pPSM1k-GL3
K Sc Mlu
Nb Sm
S M N B2
Nb Sp Bz E
pEn4PSM1k-GL3
N B2 Nb
Sp Bz E
H Sp
pEn3PSM1k-GL3
Sp H
pEn3+4PSM1k-GL3
K Sc S2
N B2 N
pOverlap3,4aPSM1k-GL3
K A Bs
Xb S
S H
RV E
pOverlap3,4bPSM1k-GL3
pRSV-GL3
K Sc
Ml

Figure 6

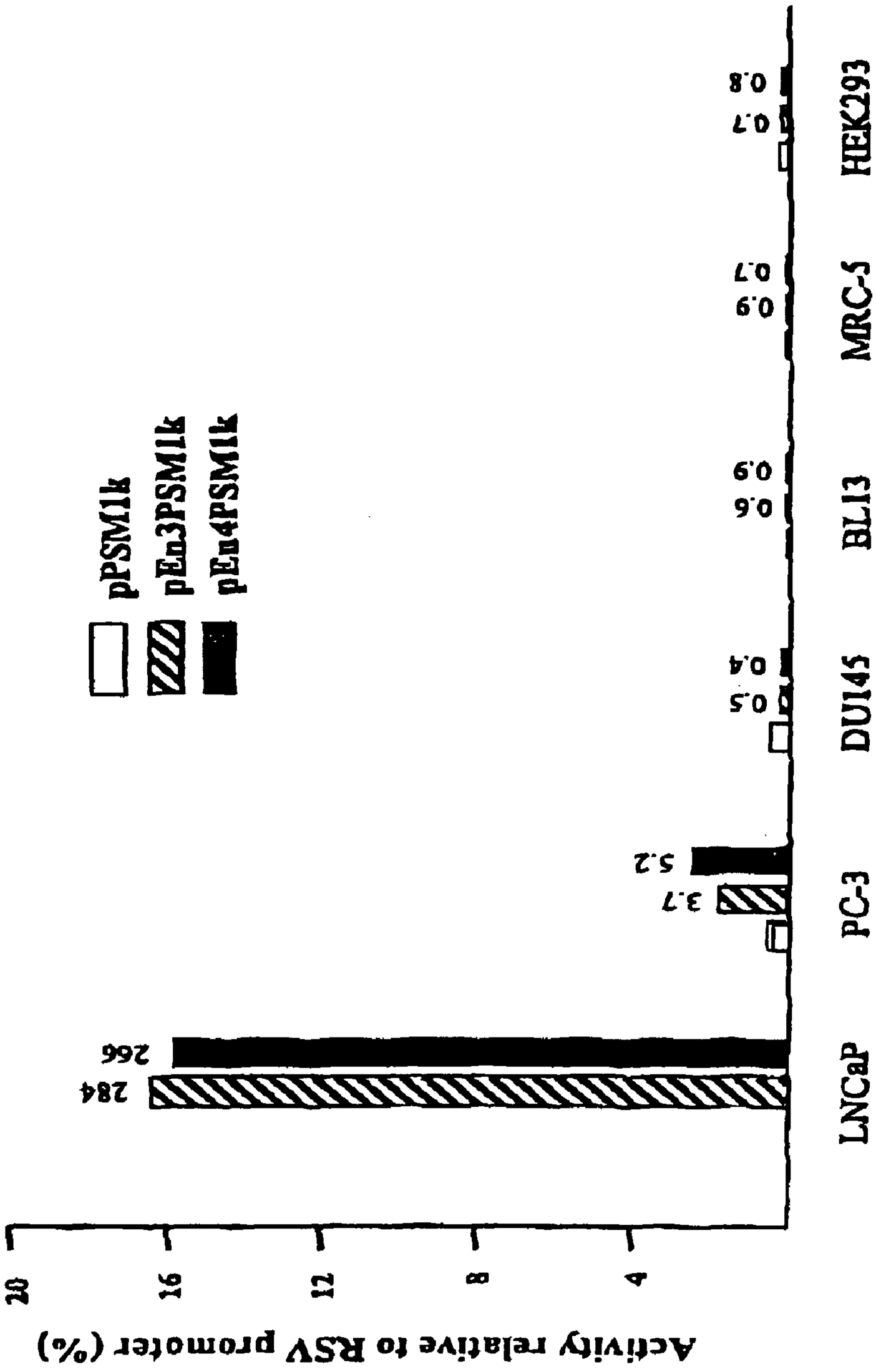
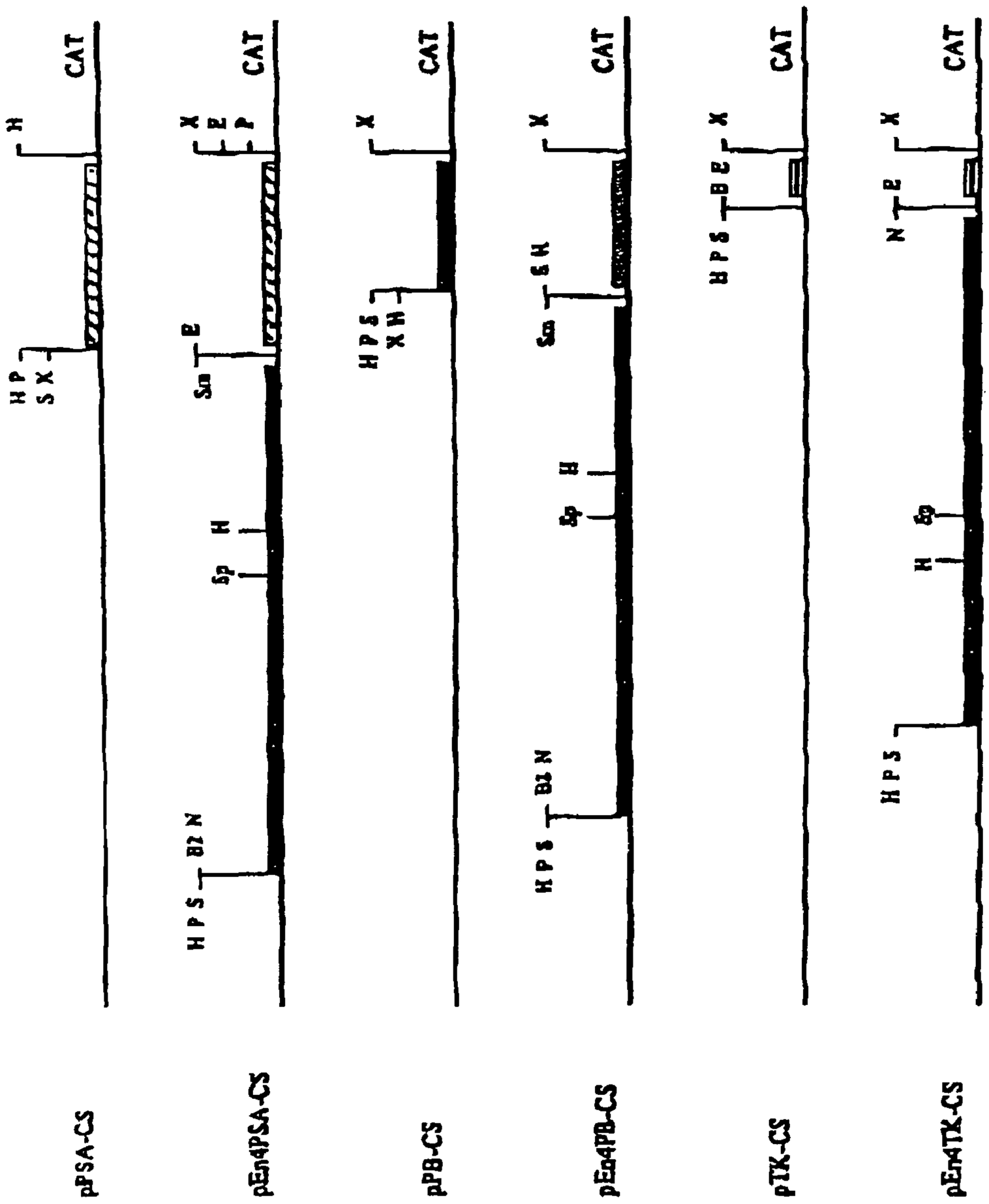

pPSM1k
pEn3PSM1k
pEn4PSM1k
LNCaP
PC-3
DU145
BL13
MRC-5
HEK293
266
284
5.2
3.7
0.5
0.4
0.6
0.9
0.7
0.9
0.7
0.8
4
8
12
16
20
Activity relative to RSV promoter (%)

Figure 7


pPSA-CS
pEn4PSA-CS
pPB-CS
pEn4PB-CS
pTK-CS
pEn4TK-CS
CAT
HP
SX
Sm
E
Sp
H
HPS
Bl N
XH
N
Figure 8

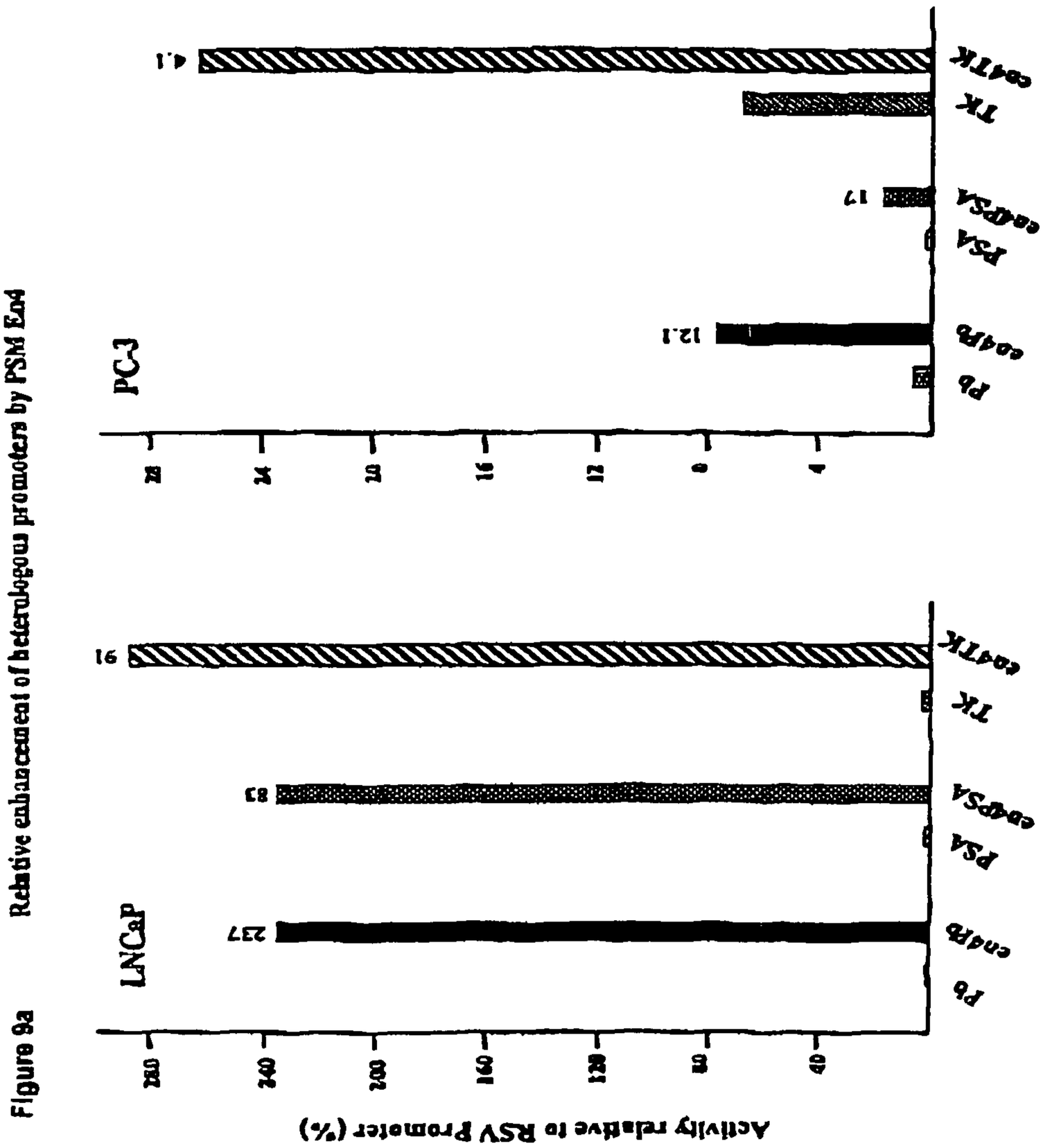

Relative enhancement of heterologous promoters by PSM Enh
PC3
91
83
17
12.1
LNCaP
237
Activity relative to RSV Promoter (%)

Figure 9a

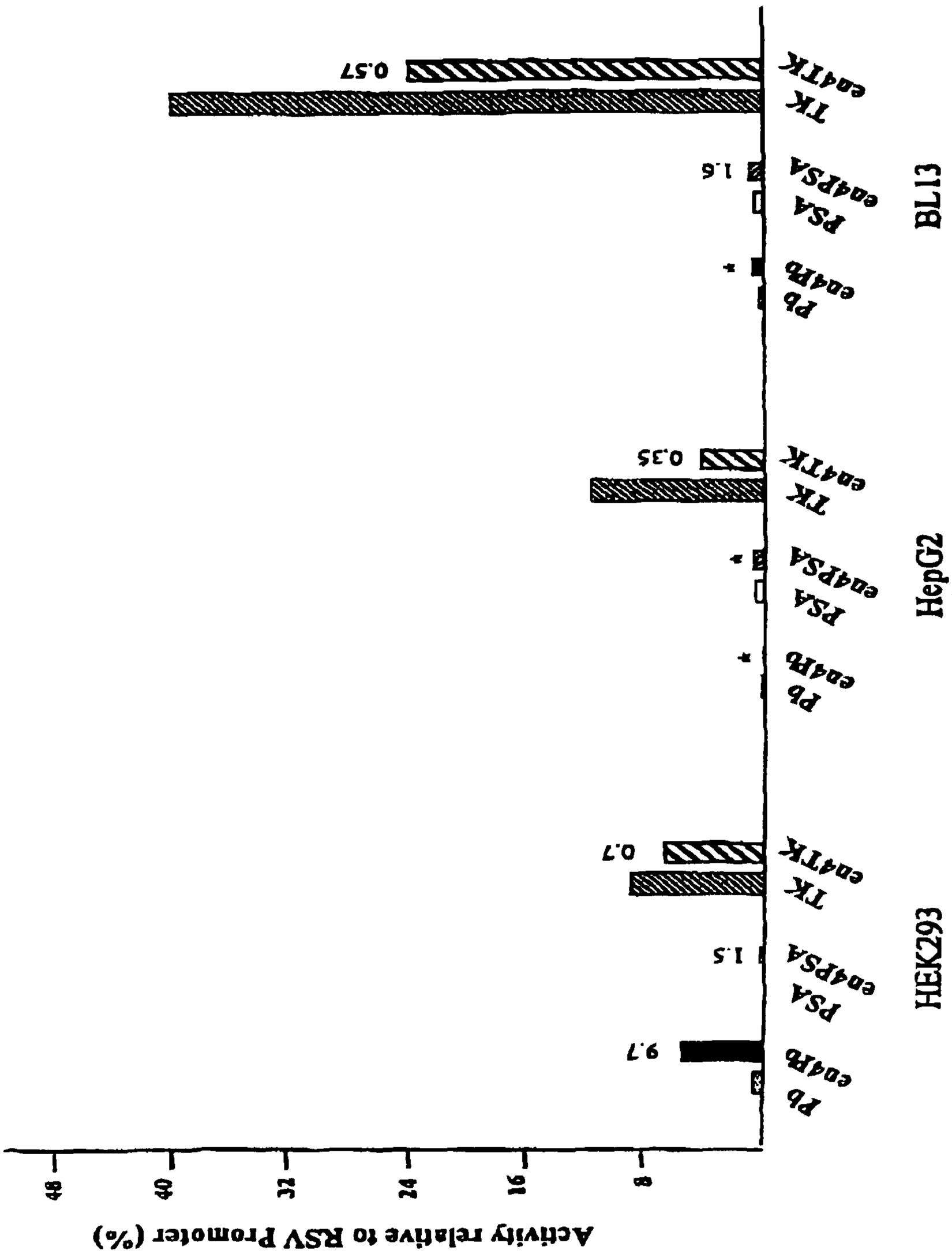

Activity relative to RSV Promoter (%)
8
16
24
32
40
48
pGL3
pGL4.10
pGL4.13
pGL4.17
pGL4.23
pGL4.27
HEK293
9.7
1.5
0.7
0.35
HepG2
1.6
0.57
BL13

Figure 9b

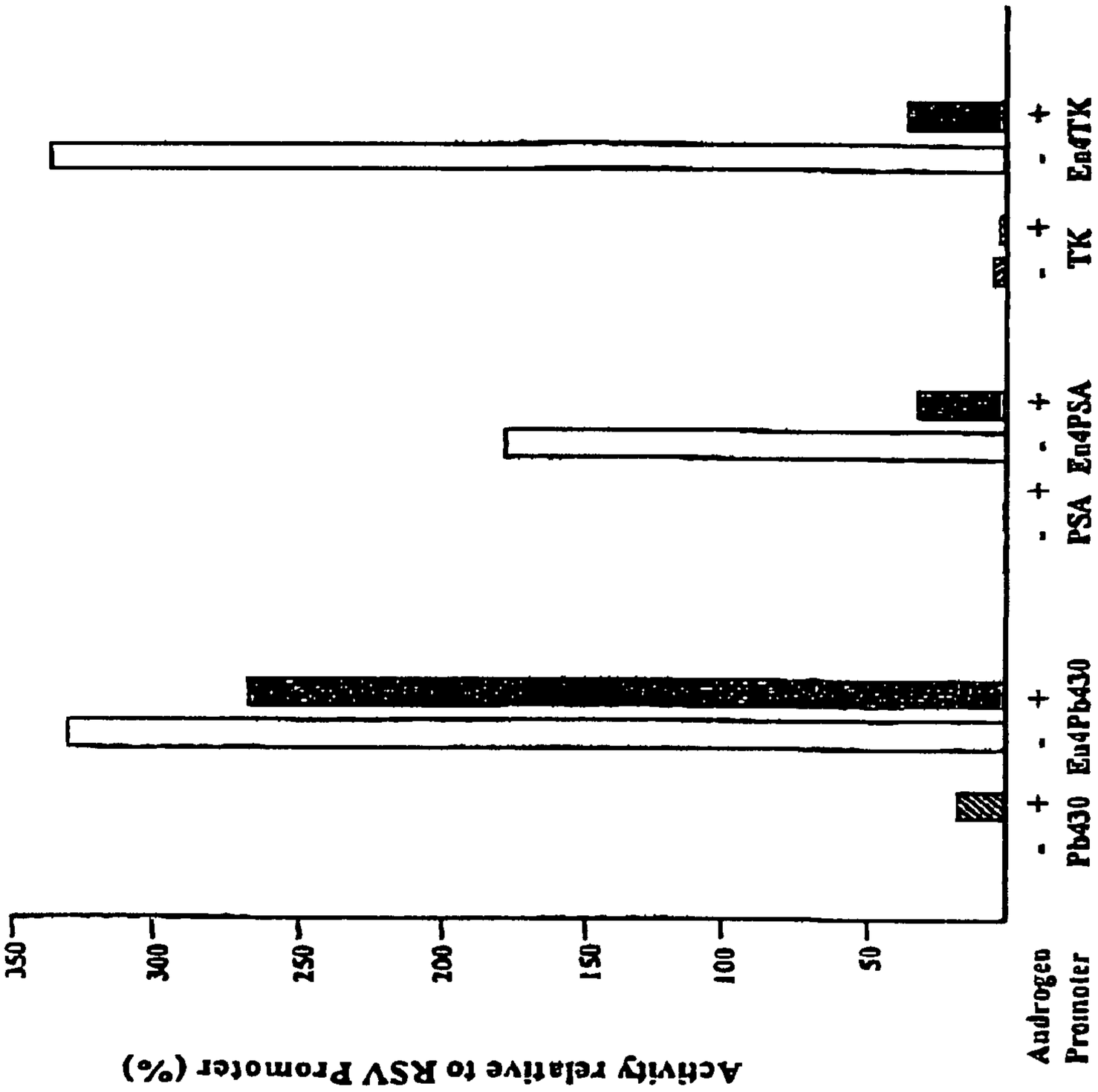

Activity relative to RSV Promoter (%)
350
300
250
200
150
100
50
Androgen Responsive Promoter
Pb430
Eu4Pb430
PSA
Eu4PSA
TK
Eu4TK
- + - + - + - + - + - +

Figure 10

Sequence of 331 base pair core region of the PSME

14760
AATTATTTTTTCCTTTAACCTTTCAAACTCAAGGAAAACCAGTTGGCCTTGACTCTGTTT
14820
GTGGAAAATTTTAAACTACTGGTTTAATTTCTTTATTGGTTGTAATATGACTATTTTACG
14880
TCATATAACAATTTTTATTGTTTGTTAAATGACTTTATTGTTTGTCATATGATAATTTTA
14940
TGTCATAGAACAATTTTTATTGCTTGATATATGACTTTATTGTTATATGGCTATACAACT
15000
AGATTTTTTTGTTGTTTTTTGACCGAGTCTTACTCTGTCACCCAGGCTGGAGTGTAATGGC
15060
ATGGTCTCAGCTCACTGCAACCTCCGCCTCCCGGG

The NdeI site 168 base pairs from the start of the core enhancer is underlined

Figure 11

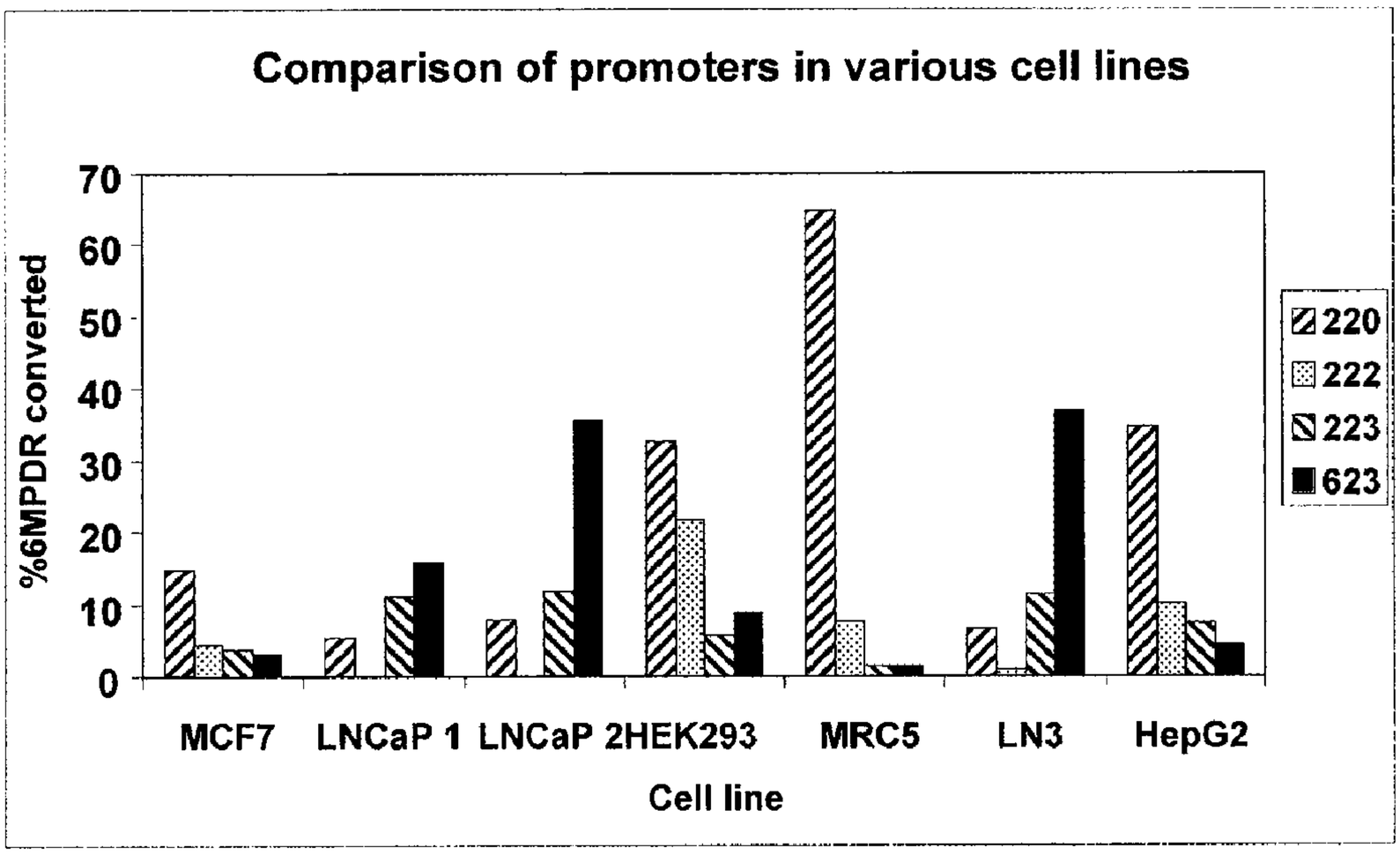

Comparison of promoters in various cell lines
%6MPDR converted
70
60
50
40
30
20
10
0
MCF7
LNCaP 1
LNCaP 2
HEK293
MRC5
LN3
HepG2
Cell line
220
222
223
623

FIG. 12

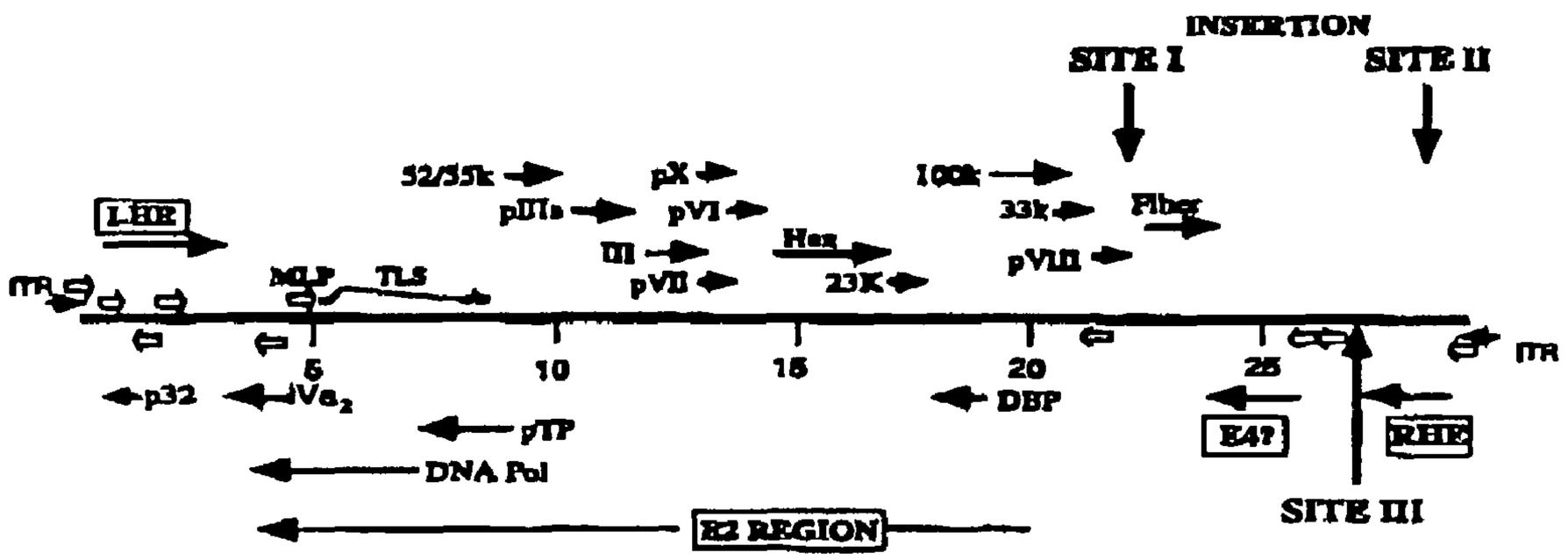

INSERTION
SITE I
SITE II
52/55k
pX
100k
pIIIa
pVI
33k
Fiber
LHR
III
Hex
pVIII
pVII
23K
MLP
TLS
ITR
5
10
15
20
25
ITR
p32
Va2
DBP
pTP
E4?
RHR
DNA Pol
SITE III
E2 REGION

Figure 13

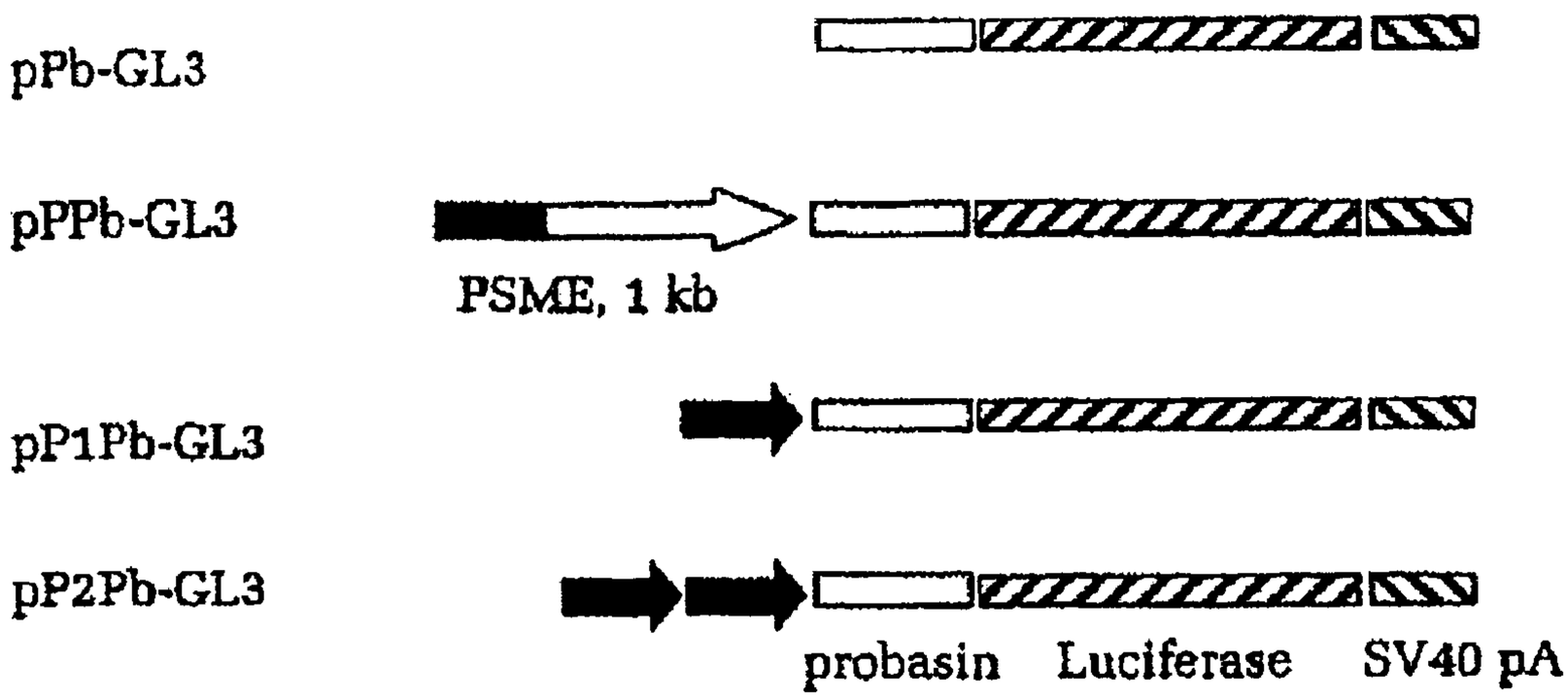

pPb-GL3
pPPb-GL3
PSME, 1 kb
pP1Pb-GL3
pP2Pb-GL3
probasin
Luciferase
SV40 pA

Figure 14

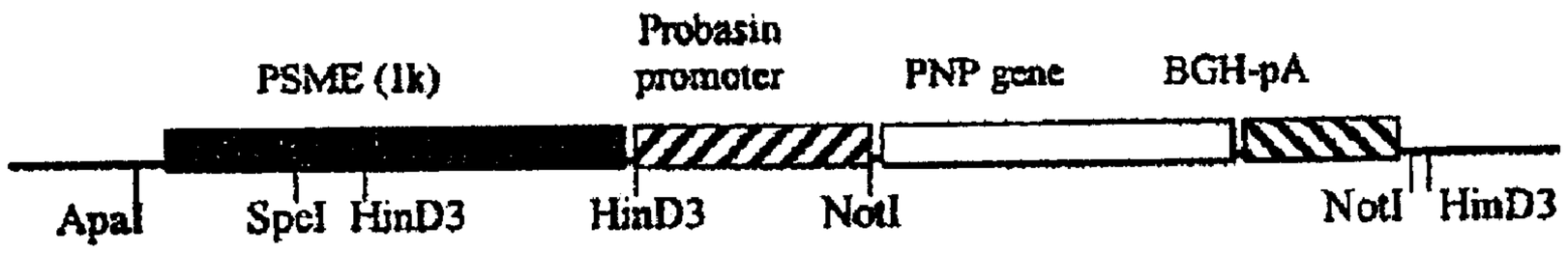

PSME (1k)
Probasin promoter
PNP gene
BGH-pA
ApaI
SpeI
HinD3
HinD3
NotI
NotI
HinD3

Figure 15

REGULATORY CONSTRUCTS COMPRISING INTRON 3 OF PROSTATE SPECIFIC MEMBRANE ANTIGEN GENE

This application is a continuation-in-part of U.S. patent application Ser. No. 09/914,651, filed on Dec. 27, 2001, now U.S. Pat. No. 7,074,400, the entire contents of which is incorporated herein. U.S. patent application Ser. No. 09/914,651 is a national stage entry under 35 U.S.C. 371 of PCT/AU00/00143, filed on Mar. 1, 2000.

FIELD OF THE INVENTION

The present invention relates to a recombinant vector comprising an ovine adenovirus genome and a sequence encoding a heterologous polypeptide. The invention also provides ovine adenovirus recombinant vectors comprising a novel regulatory element derived from a prostate specific gene. The present invention also relates to diagnostic and therapeutic methods involving the use of these vectors.

BACKGROUND OF THE INVENTION

The isolation and characterisation of DNA regions which control tissue specific and/or hormonally-regulated gene expression has been an important to the understanding of the developmental processes by which expression of particular genes is limited to specific cell types. Promoter regions are found immediately upstream and often overlapping the start site(s) of transcription and are critical for initiation and basal levels of transcription. Enhancers are regulatory regions which may lie some distance from the transcription start site, either upstream or downstream of a gene or within introns and which often confer high level tissue specific or hormonally-regulated expression; in some cases their action is specific to particular promoters. The function of both promoters and enhancers is mediated by specific proteins, transcription factors, that bind to specific DNA sequences. Alone or in combination with other transcription factors they recruit the core transcription machinery including RNA polymerase to the transcription initiation site and act to stimulate their activity. Isolated promoters and enhancer sequences can be used, in gene therapy for example, to direct expression of other genes in a cell or tissue specific manner and also provide targets for the development of agents that can specifically modulate gene expression.

The promoters and regulatory regions of a number of genes that are expressed in the prostate have been studied either using transfection techniques or by following gene expression in transgenic mice. We have previously compared the cell-type specificity of expression directed by promoters of the prostate-expressed genes, probasin (Pb) and relaxin genes and the promoter and enhancer of the prostate specific antigen (PSA) gene (1). Most of the genes identified as prostate-specific are androgen-inducible and this aspect of their function has been studied in some detail. Thus the importance of androgen response elements for induced expression and/or binding of androgen receptor have been characterised in the PSA (2,3), human glandular kallikrein (KLK2) (4), rat prostatic steroid binding proteins (PSBP) (5,6), probasin Pb (7,8) and prostatic acid phosphatase genes (9) and in regulatory elements in the introns of the rat PSBP C3(1) gene (10) and the rat 20-KDa androgen regulated protein (11).

Among the core promoter regions analysed only that of the probasin gene confers substantial prostate specificity of expression (1,15). Elements involved in conferring prostate-specificity of expression per se, as distinct from androgen responsiveness, have not been well characterised, though tissue-specific factors binding to regions of the PSBP C3 gene promoter and 1st intron have been identified (9,12). The gene for rat PSBP C(3) with 4 kb upstream and 2 kb downstream flanking sequences is expressed tissue-specifically and with appropriate hormonal control in transgenic mice (13). The use of a 5 kb upstream region from the rat PSBP C3(1) gene to express the SV40 T-antigen could elicit prostate tumours, but expression was not highly restricted and other abnormalities were common (14). Studies with transgenic mice have established that regions of the probasin and PSBP C(3) genes can confer prostate specificity.

The PSA and probasin regulatory regions are the two most studied among prostate-expressed genes. It has been established that a 430 bp region upstream of the rat probasin gene is able to confer prostate specificity of expression on reporter genes in transfection experiments (1) and in transgenic animals (15,16); when used to target expression of the SV40 T-antigen, prostate tumours develop specifically (17,18). This expression is not totally specific but specificity is significantly improved by the inclusion of MAR (matrix attachment regions) from the chick lysozyme gene (15). The 430 bp promoter region is strongly responsive to androgen induction and androgen response elements which bind the androgen receptor (AR) have been characterised (4,6,7,16).

The PSA upstream region (to-630 bp) also acts as a strongly androgen responsive promoter and androgen response elements have also been characterised (2,3). However, this region is not sufficient to direct cell type specific expression in culture (1) or tissue specific expression in transgenic mice (19). Use of the 630 bp human PSA promoter region to express an activated Ha-ras oncogene in transgenic mice led to the development of salivary gland and not prostate tumours (19). Pang et al. have reported that the equivalent promoter region isolated from a prostate cancer patient contained 7 mutations compared to the published sequence and was highly active in the prostate cancer cell line LNCaP (20,21). More recently, an enhancer region has been identified in the region 4 to 5 kb upstream of the transcription start site of the PSA gene (20,21). This PSA enhancer has been shown to act as an androgen-inducible enhancer and in combination with the PSA promoter to display significant cell-type specificity (1,20,21).

Prostate-Specific Membrane Antigen

Prostate specific membrane antigen (PSMA) is one of the few prostate-specific proteins identified whose expression is not induced by androgens.

PSMA was first identified as the antigen bound to by the monoclonal antibody 7E11-C5 (25). The antibody was raised against a membrane fraction of the prostate cancer cell line LNCaP and was shown to bind specifically to normal prostate tissue as well as primary and metastatic prostate cancer tissue. This antibody was later found to bind to an internal epitope of this membrane-bound protein (26,27). Subsequently, other monoclonal antibodies targeted to the extracellular domain of the protein have been isolated (28,29).

The cDNA encoding PSMA has been cloned and its sequence determined (30). PSMA is a Type II integral membrane protein and is associated with the plasma membrane of expressing cells such as LNCaP (30). A splice variant of PSMA (Psm') that lacks the membrane anchor domain and has been shown to be cytoplasmically located has also been identified (31). The ratio of PSMA to Psm has been reported to be increased in prostate cancer as compared with normal prostate or benign hyperplasia (31). PSMA has been shown to possess two related enzymatic activities, it acts as a carbox-

ypeptidase (folate hydrolase) on poly γ-glutamated folates (32) and as a peptidase on the acidic neuropeptide N-acetylaspartyl glutamate (33). This latter activity is consistent with the expression of PSMA or a related protein in the brain.

The specificity of PSMA expression has been studied at both the protein and RNA level. In addition to its major site of expression in the prostate immunohistochemical studies have identified PSMA expression in the duodenum brush border/small intestine, in a subset of proximal tubules in the kidney and in rare cells in the colon (34,35). All other normal issues studies have been negative for expression, except for striated muscle which stains with the 7E11-C5 antibody, but not with antibodies to the external domain of PSMA (28).

Both the 7E11-C5 and external domain antibodies have been found to react with tumour vasculature of a wide range of human tumour types (28,36), indicating specific induction of PSMA expression. PSMA expression has not been identified in any normal vasculature.

RNA expression has been found to largely parallel the protein expression data. RNAse protection analysis identified PSMA mRNA in the prostate, salivary gland and brain and sometimes in the small intestine (37). The identification of PSMA RNA in the brain is consistent with the cloning of a closely related cDNA from rat brain (33). Immunohistochemical analyses have failed, however, to identify antigenically reactive PSMA in human brain tissue.

PSMA expression has been shown to be down regulated in the presence of androgens and expression is generally elevated in late stage prostate cancer and in patients undergoing androgen deprivation or ablation therapies (37,38). Expression of PSMA has also been found to be regulated by a number of growth factors; bFGF, TGF-α and EGF upregulate expression while TNF-α decreases it (39).

The restricted high level expression of PSMA in prostate cells and the induction of its expression in the vasculature of a wide range of tumours make it ideal for the targeting of prostate and other tumour types. Genomic clones encompassing the PSMA gene have been isolated and its sequence and exon/intron structure determined (40). Regulatory regions controlling its expression may find use in gene therapeutic cancer treatments, enabling the restricted or high level expression in the target cell types. Such regulatory regions also provide a target for the development of agents that may interfere with gene expression in the target cell types.

SUMMARY OF THE INVENTION

The present invention provides a recombinant vector comprising an ovine adenovirus genome and a sequence encoding a heterologous polypeptide, wherein the sequence encoding the heterologous polypeptide is inserted between E4 and E3 transcription units of the ovine adenovirus genome.

When used herein, the PSM gene refers to the PSM genomic sequence described in O'Keefe et al, 1998 (40) (GENBANK (database of nucleotide sequences maintained by the US National Center for Biology Information) accession number AF007544) (SEQ ID NO: 2), the entire contents of which are incorporated herein by reference.

By "heterologous polypeptide" we mean a polypeptide other than the prostate specific membrane antigen (PSMA) polypeptide.

The present invention also provides a recombinant vector as hereinbefore described wherein the sequence encoding the heterologous polypeptide is inserted between nucleotides 26,682 and the 5' end of the E4 promoter of the ovine adenovirus genome. The present invention also provides that the heterologous polypeptide is inserted between nucleotides 26,682 and 26,555 of the ovine adenovirus.

The present invention also provides a recombinant vector as hereinbefore described wherein the sequence encoding the heterologous polypeptide is inserted between an ARP1 and Not1 site between the E4 and E3 transcription units of the ovine adenovirus genome.

In a preferred embodiment, the recombinant DNA molecule further comprises a promoter. Preferably, the promoter is located upstream from and is operably linked to the sequence encoding the polypeptide.

In a preferred aspect of the present invention there is provided a recombinant vector as hereinbefore described wherein the promoter is located upstream from and is operably linked to the sequence encoding the heterologous polypeptide. Preferably, the vector comprises at least one regulatory element derived from intron 3 of the PSM gene.

In a second aspect, the present invention provides a method for directing expression of a coding sequence in a cell, the method comprising introducing into the cell a recombinant vector as hereinbefore described.

In a third aspect of the present invention there is provided a method of delivering a sequence encoding a heterologous polypeptide to a target cell, the method comprising transducing the cell with a recombinant vector as hereinbefore described.

In a fourth aspect of the present invention there is provided a method of delivering a sequence encoding a heterologous polypeptide to an animal cell, the method comprising administering to an animal or animal cell a recombinant vector as hereinbefore described.

In a fifth aspect of the present invention there is provided a method of gene transfer to human cells, the method comprising administering to the cells a recombinant vector as hereinbefore described such that the vector infects at least one cell and the infected cell expresses the heterologous polypeptide.

DETAILED DESCRIPTION OF THE INVENTION

The present inventors have now found that recombinant ovine adenovirus vectors which comprise foreign genes inserted at site E3 transcription site (III), i.e. between the 3' end of the transcription unit for the Right Hand End and the promoters for the E4 region (see FIG. **13**) are surprisingly more stable than ovine adenovirus vectors which comprise foreign genes inserted at other sites.

As site III is located between transcription units, it is believed that the insertion of a discrete transcription cassette at this site is unlikely to interfere with other viral functions. Based on these results it is envisaged that the insertion of expression cassettes into the ovine adenovirus genome between coding regions of transcription units which are adjacent in ovine adenovirus genome, such as between the Left Hand End and IVa_2 transcription units, will also give rise to stable recombinant constructs.

It is preferred that the heterologous nucleic acid sequence is inserted between the Right Hand End transcription unit (i.e. E3 transcription unit) and the E4 transcription unit or between the Left Hand End transcription unit and the IVa_2 transcription unit.

In a further preferred embodiment of the first aspect, the ovine adenovirus genome is the genome of ovine adenovirus OAV287 (as described in GENBANK Accession No. U40839) or a functionally equivalent sequence.

The phrase "functionally equivalent sequence" is intended to cover minor variations in the OAV287 genome which, due to degeneracy in the genetic code, does not result in the

genome encoding different viral polypeptides. Further, this term is intended to cover alterations in the genomic sequence which lead to changes in the encoded polypeptides, but in which such changes do not substantially affect the biological activities of these viral polypeptides.

In the context of the present invention, the heterologous nucleic acid molecule (ie sequence encoding a heterologous polypeptide) may be any nucleic acid molecule of interest. For example, the nucleic acid of interest may comprise a therapeutic gene or may encode an antigenic peptide.

The therapeutic gene may be, for example, an oncogene or a tumour suppressor gene. Alternatively, the therapeutic gene may encode a product such as an enzyme, a blood derivative, a hormone, a lymphokine, an interleukin, an interferon, a TNF, a growth factor, neurotransmitter, a trophic factor, etc.

The therapeutic gene may also encode a macromolecule which complements a genetic defect in a somatic cell, or a macromolecule which catalyses one or more processes leading to cell death. Cell death may occur directly as a result of gene expression or indirectly as a result of an immune response to an expressed foreign antigen. Preferably, the gene encodes an enzyme such as herpesvirus thymidine kinase or non-mammalian cytosine deaminase which metabolizes a prodrug. More preferably the gene encodes prokaryotic purine nucleoside phosphorylase. In the presence of the appropriate prodrug, expression of the gene by the transfected cell preferably leads to metabolism of the prodrug giving rise to a toxic product which leads to cell death.

In a further preferred embodiment, the heterologous nucleic acid comprises a cell-specific promoter linked to the therapeutic gene, such that the gene is only expressed in a desired target cell. Such promoters are well known in the art. For example, for specific expression in prostate cells, the promoter may be selected from the probasin, prostate specific antigen (PSA) or prostate specific membrane antigen (PSMA) promoters. For specific expression in breast cells, the erbB-2 promoter may be used. For specific expression in lung cells, the carcinoembryonic antigen (CEA) promoter may be used.

All publications mentioned in this specification are incorporated herein by reference.

The regulatory element(s) in the vectors of the present invention may be located in either orientation anywhere within the recombinant DNA molecule or expression cassette of the present invention. For example, the regulatory element may be located downstream of the coding sequence (e.g. downstream of the 3' termination or polyadenylation signals) or within an intron located in the coding sequence. In a preferred embodiment, the regulatory element is located adjacent to the promoter. More preferably, the regulatory element is upstream of the promoter.

As the vectors of the present invention are useful for expression of proteins in vascular endothelial cells, a range of cancer types may be treated within the context of the sixth aspect of the present invention. Examples of suitable cancer types include renal cell carcinoma, transitional cell carcinoma, colonic adenocarcinoma, neuroendocrine carcinoma, malignant melanoma, pancreatic duct carcinoma, breast carcinoma, soft tissue carcinoma, non-small cell lung carcinoma, testicular embryonal carcinoma and glioblastoma multiforme. In a preferred embodiment of the sixth aspect, however, the cancer is selected from prostate, bladder or breast cancer.

As will be appreciated by those skilled in the field, the present invention provides novel regulatory elements from a gene expressed specifically in prostate, which are active both in the presence and absence of androgens.

These regulatory elements may therefore be used for high level gene expression in prostate cells. Combinations of one or more of the regulatory elements with the probasin and PSA promoters are examples of constructs that provide for high level expression with strong prostate specificity.

The regulatory elements of the present invention may also be useful for directing expression in a limited range of other cell types, including tumour neovasculature and kidney cells.

The regulatory elements of the present invention may be used to target specific expression of genes to prostate cells or tumour neovasculature or kidney cells in gene therapy.

The regulatory elements of the present invention may also be used to target specific expression of genes in the development of transgenic animal models of prostate disease.

The regulatory elements of the present invention may also be used to identify other genetic elements which are involved in the regulation of gene expression in prostate cells.

The regulatory elements of the present invention may also be used in assays to identify reagents that interfere with prostate gene expression, or to identify proteins and other factors involved in regulation of prostate gene expression.

When used herein, "high stringency" refers to conditions that

(i) employ low ionic strength and high temperature for washing after hybridisation, for example, 0.1×SSC and 0.1% (w/v) SDS at 50° C.;

(ii) employ during hybridisation conditions such that the hybridisation temperature is ≦25° C. lower than the duplex melting temperature of the hybridising polynucleotides, for example 1.5×SSPE, 10% (w/v) polyethylene glycol 6000, 7% (w/v) SDS, 0.25 mg/ml fragmented herring sperm DNA at 65° C.; or

(iii) for example, 0.5M sodium phosphate, pH 7.2, 5 mM EDTA, 7% (w/v) SDS and 0.5% (w/v) BLOTTO at 70° C.; or

(iv) employ during hybridisation a denaturing agent such as formamide, for example, 50% (v/v) formamide with 5×SSC, 50 mM sodium phosphate (pH 6.5) and 5×Denhardt's solution at 42° C.; or

(v) employ, for example, 50% (v/v) formamide, 5×SSC, 50 mM sodium phosphate (pH 6.8), 0.1% (w/v) sodium pyrophosphate, 5×Denhardt's solution, sonicated salmon sperm DNA (50, μg/ml) and 10% dextran sulphate at 42° C.

Throughout this specification, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated element, integer or step, or group of elements, integers or steps, but not the exclusion of any other element, integer or step, or group of elements, integers or steps.

In order that the nature of the present invention may be more clearly understood preferred forms thereof will now be described with reference to the following non-limiting Examples and Figures.

BRIEF DESCRIPTION OF THE FIGURES

FIG. **1**.

pPSMentrap Vector. Key features of the vector are shown: the multicloning site (MCS) unique restriction sites upstream of the PSM1k promoter region (PSM1k), leader sequence and intron (intron) derived from the pCI vector (Promega), the green fluorescent protein gene (GFP) and 3' sequences derived from the bovine growth hormone gene (bGHpA). A selection of useful restriction enzyme sites are shown; unique restriction enzyme sites are shown in bold.

FIG. **2**.

Location of cloned PSM enhancer fragments: the map shows the location of the cloned enhancer fragments within intron 3 of the PSM gene.

Base numbers (GENBANK Accession No. AF007544) are indicated for the boundaries of intron 3 and for the ends of the cloned segments. The locations of the restriction sites SmaI (Sm), HinDIII (H) and SpeI (Sp) within the intron are shown. The arrows indicate the orientation of the cloned sequences within the pPSMentrap vector (see FIG. **3**). The right hand end of the enhancer clone #1 is shown as a stippled box since this end of the clone has undergone rearrangement. The SmaI, HinDIII and SpeI sites are present in all three cloned regions.

FIG. **3**.

Promoter and enhancer inserts in pPSMentrap: The positions of the PSM 1 kb promoter region and flanking restrictions sites in pPSMentrap are shown on the top line. To the right of the promoter sequences are the leader sequence and chimeric intron and GFP reporter gene. Below are shown maps of clones containing the En3 and En4 inserts. The sequences are in opposite orientation (note order of HinDIII and SpeI sites). Restriction sites are abbreviated as follows:

B2	BglII	E	EcoRI	H	HinDIII	K	KpnI	M	MfeI	N	NsiI
Nh	NheI	P	PstI	S	SalI	Sp	SpeI	X	XbaI		

FIG. **4**.

Promoter and enhancer inserts in pCAT3SAT. Maps show the positions of the PSM 1 kb promoter, PSM En4 and the RSV promoter and their flanking restriction enzyme sites. To the right of the promoters is the leader sequence and chimeric intron and CAT reporter gene as present in the Promega pCAT3 Basic vector. Restriction enzyme sites are abbreviated as follows:

B2	BglII	Bz	BstZI	E	EcoRI	H	HinDIII	K	KpnI	M	MfeI
Ml	MluI	N	NsiI	Nh	NheI	P	PstI	S	SalI	Sc	SacI
Sm	SmaI	Sp	SpeI	X	XbaI	Xh	XhoI				

FIG. **5**.

Relative CAT expression directed by the PSM Enhancer4/PSMIk promoter. Following transfection of pPSMLK-C3S or pEn4PSM1K-C3S into the cell lines indicated normalized expression levels were determined for each construct and are expressed relative to that determined from transfection of the pRSV-C3S plasmid.

FIG. **6**.

Promoter and enhancer inserts in pGL3. Maps show the position and flanking restriction enzyme sites of the PSM 1 kb promoter (shaded boxes), PSM enhancer fragments (solid boxes) and the RSV promoter (diagonal shading) in the different constructs prepared in the pGL3 vector. To the right of the region shown is the leader and chimeric intron and luciferase reporter gene of the pGL3 vector. PEN4PSMlk-GL3 and pEn3PSmlk-GL3 contain sequences of enhancer clones #4 and #3 respectively as shown in FIG. **2**. pEn3+4PSMlk-GL3 contains PSM enhancer sequences encompassing bases 14,045 to 16,575 (see FIG. **2**). POverlap3, 4aPSMlk-GL3 and pOverlap3, 4bPSMlk-GL3 contain enhancer sequences from bases 14,760 to 15,804, the a and b constructs containing the enhancer sequences in opposite orientations as indicated by the position of the HinDIII and SpeI sites.

Restriction enzyme sites are abbreviated as follows:

A	ApoI	B2	BglII	Bz	BstZI	E	EcoRI	Eo	EcoO1091	H	HinDIII
K	KpnI	M	MfeI	Ml	MluI	N	NsiI	Nh	NheI	Nt	NotI
P	PstI	RV	EcoRV	S	SalI	Sc	SacI	Sc2	SacII	Sm	SmaI
Sp	SpeI	X	XbaI	Xh	XhoI						

FIG. **7**.

Relative luciferase expression of PSM enhancer/promoter constructs in the pGL3 vector. Mixtures of luciferase reporter plasmids (1.5 μg) and the normalizing plasmid pRSV-CAT (1 μg) were transfected into different cell lines as shown. Normalized luciferase expression was determined and activity of the different plasmids expressed relative to the normalized expression from pRSV-GL3. Numbers above the columns indicate the relative enhancement of activity compared with expression from the PSM promoter alone construct, pPSMlk-GL3.

FIG. **8**.

PSM enhancer constructs with other promoters. Maps show the positions and flanking restriction enzyme sites of the PSM enhancer sequences (En4, solid boxes), and promoters from the PSA (diagonal pattern), probasin (vertical pattern) and thymidine kinase (horizontal pattern) genes. To the right of the promoters is the CAT reporter gene of the pCATSAT vector. Restriction enzyme sites are abbreviated as follows:

B	BamHI	B2	BglII	E	EcoRI	H	HinDIII	N	NsiI	P	PstI
S	SalI	Sm	SmaI	Sp	SpeI	X	XbaI				

FIG. **9**.

Relative enhancement of heterologous promoters by PSM En4.

a. Prostate cell lines

b. Non-prostate cell lines

The different promoter and enhancer constructs were transfected into cell lines as shown and CAT reporter gene expression normalized against SAT expression determined. Activities are expressed as a percentage of the normalized expression of pRSV-CAT. Numbers above the columns indicate the relative enhancement of activity compared with expression from the respective promoter alone constructs. An * indicates that expression levels were too low to determine a ratio.

FIG. **10**.

Effect of androgen on enhancement of heterologous promoters by PSM En4. Plasmids containing the different enhancer/promoter combinations as indicated below the graph were transfected into LNCaP cells that were maintained in medium that had been charcoal stripped to remove androgens or in equivalent medium to which the non-metabolizable androgen analogue R1881 had been added to 0.28 nM.

The presence or absence of androgen is also indicated (– or +) below the graph. Activities were determined and expressed as described in FIG. **9**.

FIG. **11**.

Sequence of 331 base pair core region of the PSME (SEQ ID NO: 1).

FIG. **12**.

Specificity of purine nucleoside phosphorylase (PNP) gene expression in viral constructs OAV223 and OAV623 (PSME and probasin promoter), OAV220 (PSME and RSV promoter) and OAV222 (PSME and CMV promoter).

FIG. **13**

Structure of the OAdV genome showing the sites for insertion of foreign gene cassettes.

FIG. **14**

Structure of a series of constructs prepared in which the probasin promoter, with or without PSM enhancer fragments was subcloned in front of the luciferase reporter gene in the pGL3 vector.

FIG. **15**

Map of a construct in which the pGEM11 plasmid in which the PNP gene was placed under the control of the 1 kb PSME region (bases 14760 to 15804 in reverse orientation) adjacent to the 430 bp probasin promoter.

EXPERIMENTAL DETAILS

Example 1

Isolation of PSMA Gene Enhancer Sequences

Analyses of the region upstream and encompassing the transcription start site of the PSMA gene (40) has shown that a 1 KB region directs expression of reporter genes in the prostate cell line LNCaP. This expression shows specificity for prostate cells when compared to that directed by the SV40 enhancer/promoter. Expression in LNCaP cells was about 75% of that directed by the SV40 enhancer/promoter. Comparison with another widely expressed promoter, that of the Rous sarcoma virus (RSV) has indicated that the SV40 enhancer/promoter is only very weakly active, <1% of RSV activity, in LNCaP cells (unpublished data). We have cloned regions encompassing up to 11 kb of sequences 5' to the PSMA transcription start site and tested their ability to provide increased reporter gene expression; no increased activity was seen relative to the 1 kb promoter region.

A strategy was developed to allow screening of DNA fragments for their ability to enhance transcription directed by the 1 kb proximal promoter region of the PSMA gene. The 1 kb promoter was cloned in front of the Green Fluorescent Protein (GFP) gene in the plasmid vector pPSMentrap shown in FIG. **1**. Upstream of the promoter was inserted a polylinker region containing sites for cloning candidate fragments.

pPSMentrap contains the following elements: a polylinker containing restriction sites for the enzymes KpnL, HinDIII, SalI, MfeI, NsiI, BglI, NheI and SpeI, the PSMA promoter region stretching from base 1386 base 2560 (XbaI site) of the PSMA sequence (GENBANK Accession No. AF007544), a chimeric intron as contained in the pC1 vector (Promega), the GFP gene, the 3' end polyadenylation signal from the bovine growth hormone gene and the plasmid backbone (including ampicillin resistance gene and origin of replication) from the pC1 vector.

A library of DNA sequences was prepared by digesting the bacteriophage P1 cosmid P1-683 which contains the 5' half and upstream flanking sequence of the PSMA gene (40). Cosmid DNA was digested for various of times with the enzyme Tsp509I which cuts at AATT sites generating a range of partial digestion products. These were separated by agarose gel electrophoresis and fragments in the size range 1 to 2 kb recovered and cloned into the MfeI site of the pPSMentrap vector. A library of about 600 individual clones was picked.

Clones were grouped into 12 pools of 49 and DNA prepared from each pool using Qiagen columns and protocols. DNA (2.5 mg) from each pool was transfected into LNCaP cells in 3.5 cm dishes as previously described (1). After 48 to 72 hours, cell cultures were examined under a UV fluorescence microscope to identify any fluorescing cells. Positive pools were split into 7 by 7 matrices and DNA preparations made from the 7 clones in each row and each column. The transfections were repeated to identify positive sub-pools. Clones at the intersections of positive rows and columns were further screened individually to verify the expression of GFP. The three clones giving the strongest signals, #1, #3 and #4 were taken for further analysis.

Example 2

Location and Sequence Analysis of Enhancing Fragments

The inserts from the clones were re-cloned into PBLUESCRIPT SK+ (pBKSEn3 and pBKSEn4) cloning vectors and the sequences of their ends determined. All clones were found to originate from the third intron of the PSMA gene as shown in FIG. **2**. The positions of both ends of clones #3 and #4 were identified as shown. The inserts in clones #3 and #4 were aligned in opposite orientations relative to the PSM promoter in the pPSMentrap vector as shown in FIG. **3**. The clones share a common overlapping sequence of 1044 bp and extend in total over 2,530 bp. The third clone, #1, derived from the same region, one end being 6 bp upstream of the end of clone #4 and it also contained the SpeI and HinDIII sites contained in the region common to clones #3 and #4. It had, however, undergone some rearrangement on cloning and has not been further studied.

Example 3

Function of PSMA Enhancer Region

The activity of the PSMA enhancer region was first identified by visual inspection of fluorescence intensity of cells transfected with clones carrying PSMA gene inserts upstream of the PSM promoter. In these preliminary experiments it was also noted that the enhancer (clone #4) did not appear to function in the bladder cell line BL13 (not shown). In order to provide for quantitative determination of promoter and enhancer function, enhancers #3 and #4 (hereafter designated En3 and En4) in combination with the PSM 1 kb promoter were re-cloned into two different gene expression reporter systems.

Example 4

Expression Assayed in the pCAT3SAT System

The pCAT3SAT vector contains a modified bacterial chloramphenicol acetyl transferase reporter gene for determining promoter activity and a reference reporter gene, serine acetyl transferase, under the control of the RSV promoter in order to standardise CAT expression for transfection efficiency. It was prepared by cloning the serine acetyl transferase reporter gene from the pCATSAT plasmid (1) as a

SalI/BamHI fragment into BamHI, SalI cut pCAT3 vector (Promega). Constructs, pPSMlk-C3S and pEn4PSMlk-C3S, containing the PSM promoter with or without the PSM enhancer fragment 4 (En4) were prepared by cloning the PSM enhancer/promoter fragments as SalI/PstI fragments from the pPSMentrap vector into pCAT3SAT cut at the XhoI and PstI sites in the polylinker upstream of the CAT gene (FIG. **4**). A control construct containing the RSV promoter, pRSV-C3S, was also prepared by blunt end ligation of a NaeI to SacI fragment from pCATSAT (1) into the NheI site of pCAT3SAT (FIG. **4**). Cell lines were transfected with the different constructs and CAT and SAT activities determined after 48 h as described (1). The normalized expression data are shown in FIG. **5**.

In LNCaP cells an enhancement of expression of approximately 50 fold (from 0.33% to 15.7% of the activity of the RSV promoter) was seen when the En4 fragment was present upstream of the 1 kb PSM promoter. This expression showed a high level of specificity for LNCaP cells that express PSMA. Another prostate cell line, PC3, showed very low levels of expression from the PSM promoter either in the presence or absence of the enhancer. No expression above background was seen for three non-prostate cell lines (MCF-7, a breast cancer line, human embryonic kidney cells (HEK293) and the liver line HepG2). Low and variable expression was seen in a second breast cancer cell line T47-D2, with the enhancer/promoter construct showing about 10% of the activity seen in LNCaP cells.

Example 5

Expression Assayed in the Luciferase pGL3 System

Because of the low activity of the PSM 1 KB promoter in the CAT assay system, promoter and enhancer sequences were cloned into the pGL3 vector (Promega) which contains the luciferase reporter gene. The structure of the clones is shown in FIG. **6**. pPSMlk-GL3 and pEn4PSMlk-GL3 were prepared by cloning KpnI to XbaI fragments from pPSMlk-C3S and pEn4PSMlk-C3S respectively into pGL3 cut with KpnI and NheI. pEn3PSMlk-GL3 was prepared by cloning the KpnI to NheI enhancer fragment of pEn3PSMentrap into pEn4PSMlk-GL3 cut with KpnI and NheI. To assay activity, mixtures of each pGL3 construct and the reference plasmid pRSVCAT (1) were transfected into a variety of cell lines by standard procedures as described previously (1). DNA concentrations were determined by image analysis of ethidium bromide stained gels and master mixes prepared in the ratio of 1.5 μg of pGL3 construct to 1 μg of pRSVCAT. The same master mixes were used for transfections into all cell lines. Cells were transfected with 2.5 μg of DNA mixes using standard procedures (1) and expression assayed after 48 hr. Extracts were prepared and luciferase activity determined using the Luciferase Assay System (Promega).

CAT activities were determined as previously described. Luciferase expression levels were standardised with respect to the pRSVCAT reference plasmid and then standardised activities expressed as a proportion of that of pRSV-GL3/pRSVCAT (FIG. **7**).

In LNCaP cells expression from the PSM 1 k promoter was strongly enhanced by both En3 and En4 enhancer sequences (about 260 fold) with expression levels directed by pEn3PSMlk and pEn4PSMlk being 15 and 15.7% that of the RSV promoter. In the non-PSMA-expressing prostate cell line PC3 a low level of enhancement (3.7 and 5.2 fold for En3 and En4 respectively) was seen, while there was no enhancer function in the other non-expressing prostate line, DU145. For a range of non-prostate cell lines tested, HepG2 liver cells, MRC5 primary lung fibroblasts, BL13 bladder carcinoma and human embryonic kidney HEK293 cells, essentially no activity was seen for the PSMA enhancer/promoter or promoter alone constructs. Activity is thus highly specific for the expressing prostate cell line LNCaP with partial enhancer function in one non-expressing prostate cell line PC-3.

Example 6

Characterisation of the Enhancer Element

To determine the extent of sequences required to provide enhancer activity a construct was prepared that contained all the sequences encompassed by clones En3 and En4 as well as constructs containing the overlapping region present in both cones (see FIG. **6**). pEn3+4PSM1k-GL3 was prepared by cloning a KpnI to NdeI restriction fragment from pBKSEn3 into pEn4PSM1k-GL3 cut with KpnI and NDEI. Clone pOverlapen3/4a was prepared by cloning the San to HinDIII fragment from pEn3PSMentrap into PBLUESCRIPTSK+ cloning vector, subsequently cloning the HinDIII fragment from pEn4PSMentrap into the HinDIII site of the intermediate vector and verifying that it was in the correct orientation. The overlapping enhancer fragment was then cloned as a KpnI to EcoRI fragment in front of the PSM 1 kb promoter in pPSMlk-GL3 cut with KpnI and EcoRI. A construct with the overlapping region in the opposite orientation relative to the PSM promoter was likewise prepared by first cloning the SalI to HinDIII fragment from pEn4PSMentrap into PBLUESCRIPTSK+ cloning vector followed by the HinDIII fragment from pEn3PSMentrap and then cloning the overlap region in front of the PSM promoter as a KpnI to EcoRI fragment.

The effectiveness of these constructs was compared with that of the PSMlk promoter alone and the EN4/PSMlk promoter by transfection (as above) into LNCaP cells. Clones containing either orientation of the overlap region gave rise to expression levels similar to those containing En 4 sequences. The construct containing the whole region encompassed by enhancers 3 and 4, however, gave significantly stronger expression. The level of expression was about half that of the RSV promoter.

Example 7

PSMA Enhancer Action on Other Promoters

The properties of the enhancer were further assessed by linking it to other promoters, both those active primarily in prostate cells, PSA and probasin, and a non-tissue-specific promoter, that of the herpesvirus thymidine kinase gene (TK). The structures of these promoter regions are shown in FIG. **8**. For the PSA and probasin constructs the enhancer region, En4, was cloned as an NheI fragment from the pEn4PSMlk-C3S plasmid into the XbaI-cut plasmids pPSA630 CATSAT and pPb430 CATSAT respectively (by partial digestion with XbaI for the probasin construct). pPSA630CATSAT and pPb430 CATSAT have been described previously (1). The plasmid pTKCATSAT. 1 was prepared by cloning the TK promoter region, bases −101 to +59, as a SalI to XhoI fragment into the SaII-cut vector pCATSAT. 1 (1) [pCATSAT. 1 is a derivative of pCATSAT (1) in which SalI, PstI and XhoI sites present upstream of the RSV promoter were removed or destroyed by XhoI and partial SalI digestion and religation]. pEn4TKCATSAT was prepared by cloning the SalI to BglII

enhancer-containing fragment from pEn4PSMentrap into pTKCATSAT. 1 cut with SalI and partially cut with BamHI.

All six plasmids were transfected into a number of cell lines and CAT and SAT reporter gene expression determined as described (1). Expression levels were standardised against that of the RSV promoter determined by transfection of a standard mixture of pRSVCAT and pRSVSAT plasmids as described (1). Results are shown in FIGS. **9***a* & *b*.

In LNCaP cells strong enhancement of the PSA, probasin and TK promoters was seen, with that for probasin being strongest. Levels of expression for all enhancer constructs were 2 to 3 times that of the RSV promoter. Since all promoters achieved similar levels of expression in the presence of the enhancer the "fold-enhancement" shown probably reflects differences in the level of non-enhanced expression from the different promoters.

In PC3 prostate cells, which do not express PSMA, much reduced enhancement was seen, being 5 to 16 fold for the different promoters. This is similar to the results seen when the enhancer was joined with its own PSM promoter. Thus it appears that PC3 cells contain some factors that can interact with the PSM enhancer to activate transcription, but lack others, or do not have sufficient levels, to enable full enhancer function as is seen in LNCaP cells.

For the non-prostate cell lines, no enhancement was seen in HepG2 liver or BL13 bladder cells. Enhancement was seen in the embryonic kidney HEK293 cells. Low level enhancement (1.4, 1.5 fold) was seen for the PSA and TK promoters, while there was a stronger 9 fold enhancement of the probasin promoter. No enhancement by En4 of its homologous PSM promoter was seen in HEK293 cells (FIG. **7**). Since the proximal kidney tubules are a site of low level PSMA expression, the expression seen in HEK293 cells may be biologically meaningful.

Example 8

PSM Enhancer Function does not Require Androgens

The androgen requirement for activity of the PSM enhancer (En4) was studied when it was linked to two highly androgen-inducible promoters, those of the probasin and PSA genes and one constitutive promoter, TK. LNCaP cells were transfected with plasmid constructs using media that had been charcoal stripped to remove androgens. Cells were maintained in androgen-free medium or incubated in the presence of the non-metabolizable androgen analogue, R1881 added to 0.28 nM (1). For all promoters strong enhancement of expression was seen whether or not androgen was present in the medium.

However, for all three constructs containing the PSM enhancer the level of expression actually decreased upon androgen addition. This suggests that the enhancer may contain sequences mediating the observed androgen-suppression of the endogenous PSMA gene.

Example 9

Sequences Required for Enhancer Function

In order to determine what sequence regions were critical for enhancer function a series of constructs were prepared in which different fragments from the PSME region were placed in front of the PSM promoter in the pPSMlk-GL3 plasmid. The sequences included in each construct are shown in the table below. The orientation of the enhancer sequences relative to the promoter is indicated as either F (forward, as for pEn4PSMlk-GL3) or R (reverse, as for pEn3PSMlk-GL3). Activity of these constructs was assayed following transfection into LNCaP cells along with the pRSVCAT control plasmid. Extracts were prepared and assayed 48 hr after transfection, luciferase activity normalized using the activity of the co-transfected pRSVCAT plasmid and expressed relative to that of pRSV-GL3 (Table below).

Construct	Enhancer sequences	Activity in LNCaP cells (% RSV)
pPSMlk-GL3		0.2
pEn4PSMlk-GL3	14760-16575 F	16.0
pEn3PSMlk-GL3	14045-15804 R	15.7
pEn3 + 4PSMlk-GL3	14045-16575 F	39
pEn3/4aPSMlk-GL3	14760-15804 F	25
pEn3/4bPSMlk-GL3	15804-14760 R	21
pEn4Sal/HindIIPSMlk-GL3	14760-15374 F	20
pEn3Sal/HindIIIPSMlk-GL3	15804-15369 R	0.1
pEnO2/770SpeIPSMlk-GL3	14760-15530 F	24
pEnO2/2/592NsiIPSMlk-GL3	14760-15352 F	22
pEnO2/445MscIPSMlk-GL3	14760-15205 F	18
pEnO2/331SmaIPSMlk-GL3	14760-15091 F	26
pEnO2/168NdeIPSMlk-GL3	14760-14930 F	6
pEnO1/722SmaIPSMlk-GL3	15092-15804 R	0.3
pEnO1/886NdeIIPSMlk-GL3	14925-15804 R	0.4

These data indicate that most of the enhancer activity is contained within the 331 bp region encompassing bases 14760 to 15091. This region shows similar activity (26% that of RSV) to the En3 and En4 clones and to the approximately 1 kb region shared between them. Deletion from the 1 kb overlap region of either the left half or the entire 331 bp region (constructs pEnO1/722smaIPSMlk-GL3 and pEnO1/886NdeIIPSMlk-GL3) eliminates enhancer activity, showing that this region is essential for activity. Elimination of the right half of the 331 bp region, leaving just 170 bp covering bases 14760 to 14930, leads to a marked reduction in activity.

Thus bases 14760 to 14930 are essential for PSME function, but sequences extending from 14760 to 15091, provide for much stronger enhancer activity. The sequence of the region is shown in FIG. **11**.

Example 10

PSME Core Enhancer Region Retains Cell-Type Specificity

Experiments were carried out on the 331 bp core region of the PSME that provides for enhancer function (bases 14760 to 15091) to determine whether this region retained its cell-type specificity. The activity of plasmids pPSMlk-GL3, pEn02/331SmaIPSMlk-GL3 and pRSV-GL3 was assayed after transfection into a number of cell lines (Table below). Plasmids were co-transfected with an internal control pRSVCAT plasmid, extracts prepared and assayed 48 h after transfection. Luciferase activities were normalized using the activity of the pRSVCAT plasmid and are expressed relative to that of pRSV-GL3.

	Activity Relative to the RSV promoter (%)				
Construct	PC-3	DU145	MCF7	MRC5	HepG2
pPSMlk-GL3	0.45	0.21	0.12	0.032	0.033
PEn02/33 lSmaIPSM1k-GL3	1.70	0.13	0.14	0.048	0.022

As for the longer enhancer fragments, partial enhancer activity was seen in the PC-3 prostate cancer cell line that does not express PSMA. For the other non-PSMA expressing

prostate cell line, DU145, no enhancement of basal promoter activity was seen. Likewise the 331 bp PSME core region is not functional in three non-prostate cell lines. The core region thus retains the specificity of the PSME.

Example 11

Tandem Enhancer Sequences Provide for Greater Activity

A series of constructs were prepared in which the probasin promoter, with or without PSM enhancer fragments was sub-cloned in front of the luciferase reporter gene in the pGL3 vector. The structure of the constructs is shown in FIG. **14**. The 430 bp probasin promoter fragment has been described previously (1) and was re-cloned from the pPB-CS plasmid (see FIG. **8**). pPPb-GL3 contains the 1 kb overlapping enhancer region (bases 14760 to 15804). pP1Pb-GL3 and pP2PPb-GL3 contain one or two copies respectively of the 331 bp enhancer region (bases 14760 to 15091). All enhancer sequences are in the forward orientation.

The constructs were transfected, along with an RSVCAT control plasmid, into LNCaP, HEK293 or MCF-7 cells and expression measured in cell extracts prepared after 48 h incubation. Transfections were done in androgen-depleted media and luciferase activity corrected using the co-transfected RSVCAT internal control.

Relative Luciferase Activity			
	LNCaP	HEK293	MCF-7
pPb-GL3	1.45	2.36	0.36
pPPb-GL-3	246	2.17	1.09
pP1Pb-GL-3	346	3.2	0.73
pP2Pb-GL-3	798	1.8	5.75
pRSV-GL-3	318	277	107

Greatest expression in LNCaP cells is seen with the double enhancer construct, being 2 to 3 times greater than those constructs with a single copy of the enhancer. Specificity of expression is largely maintained in these transfection studies, though the pP2Pb-GL3 construct shows an elevated level of expression in MCF-7 cells.

Example 12

Enhancer Function in a Viral Backbone

The properties of the PSME combined with the probasin promoter (its high activity and specificity and limited responsiveness to androgen levels) are particularly suitable for directing prostate-specific gene expression in gene therapy applications.

The *E. coli* purine nucleoside phosphorylase (PNP) gene in combination with the pro-drugs fludarabine or 6-methylpurine 2-deoxyriboside (6 MPDR) can be used to deliver enzyme pro-drug therapy (41). An expression cassette was prepared in the pGEM11 plasmid in which the PNP gene was placed under the control of the 1 kb PSME region (bases 14760 to 15804 in reverse orientation) adjacent to the 430 bp probasin promoter. A map of this construct (pPPP (for Psm/Probasin/PNP)) is shown in FIG. **15**. The cassette in pGEM11 was partially sequenced to confirm its structure

The expression cassette was subcloned by cutting with ApaI and NotI (partial digest for NotI) and inserting into ApaI/NotI cut ovine adenovirus (OAV) vectors (42). The expression cassette was inserted into two separate sites in the OAV plasmid. One isolate was prepared by cloning into OAV200 cut with ApaI and NotI (Site 1) to give clone pOAV223. In the other isolate, pOAV623, the cassette was cloned in an alternate site (Site 3) of the plasmid POAV600 (42). Plasmid DNA was transfected into CSL503 cells as described (43) and viruses OAV223 and 623 recovered.

OAV223, OAV623 and two other viruses OAV220 and OAV222, that are equivalent to OAV223 except that the PNP gene is under the control of the RSV and CMV promoters respectively, were used to infect a variety of cell types as shown in FIG. **12**. Cells were infected with the different viruses at a multiplicity of infection of 10^3 opu/cell and PNP expression measured after 4 days (44). For each cell type an amount of lysate was used such that PNP expression from the most strongly expressing virus fell within the linear range of the assay. Thus, the absolute amount of PNP activity cannot be compared between cell lines but ratios of expression can be compared.

The data presented in FIG. **12** show that in the context of the viral backbone and OAV infection strong specificity of gene expression is maintained. Highest activity is seen from OAV623, then OAV223, being greater than that of the RSV promoter in LNCaP and LN3 prostate cancer cells. In all the non-prostate cell lines the RSV promoter (OAV220) provides strongest expression. The differential specificity of the PSME/Pb promoter versus the RSV promoter for prostate compared to non-prostate cells ranges from expression about 15 fold for HEK293 and MCF-7 through to 200 fold for MRC-5). Thus, in some cell types specificity is reduced in the OAV context but it is still substantial. In the following example retention of cell specificity of the PSME in combination with its own PSM promoter is also demonstrated when carried by a human adenovirus Type 5.

Example 13

Enhancer Function in Human Umbilical Artery Cells

PSMA has been shown to be expressed in the neovasculature of a range of tumour types, but not in normal vasculature. We have determined, using reverse transcriptase PCR, that PSMA is expressed in endothelial cells derived from the human umbilical artery (HUAECs) (data not shown). Other genes that are up-regulated in tumour vasculature are also expressed in HUAECs and related human umbilical vein cells (HWECs), e.g. endoglin (45). Function of PSM regulatory sequences was therefore examined in these cells. The activity of the PSME coupled to the PSM 1 kb promoter was evaluated using a replication-defective adenovirus, human adenovirus Type 5, into which the expression cassette from the pPSMen-trap vector with the En4 insert had been inserted. The virus, Ad525, carries the GFP gene with bovine growth hormone 3' polyadenylation sequences under the transcriptional control of PSME En4 sequences coupled to the PSM 1 kb promoter. A control virus, Ad526, in which the GFP gene was under the control of the ubiquitously-active EF-1 promoter was also used.

HUAECs and HUVEGs were dissociated from umbilical arteries and cultured as described by Underwood and Bean (46) except that tissue culture dishes were coated with bovine, rather than chicken, fibronectin. HUACs, HUVECs, LNCaP and control human lung fibroblast MRC-5 cells were plated at 4×10^4 cells per chamber in fibronectin-coated microscope slide chambers. The following day they were infected with 5×10^8 optical particle units per chamber of either Ad525 or

Ad526. Expression of the GFP gene was monitored by fluorescence microscopy 3 days after infection for the control Ad526 virus and after 6 days for the PSME driven Ad525.

Expression from the control virus (EIF, OAV526) was strong in all cell types. For the En4PSMGFP virus, clear expression was seen in HUAECs and LNCaP cells, weaker expression in HUVECs, but no expression could be detected in MRC-5 cells. The combination of PSME and the PSM promoter is thus able to specifically drive gene expression in these arterial cells that express the endogenous PSM gene and should prove useful in directing expression to tumour vasculature.

Example 14

Construction and Stability of OAdV Expressing Green Fluorescent Protein

The plasmid pOAdV217A, containing the HCMV/GFP cassette in site I was constructed as follows. The coding portion of the GFP gene was blunt-cloned into the XhoI/SmaI sites of plasmid pCI (Promega Corp, Madison Wis.) to place it under the control of the HCMV promoter. The entire cassette was excised by BglII/BamHI digestion and blunt-cloned into the XbaI site of pGem11zf (Promega Corp, Madison Wis.). A clone with a 5' ApaI and 3' NotI site was selected and the insert was cloned into these sites in pOAV200 (site I insertion) for virus rescue (Vrati et al., 1996b). Subsequently, the cassette was further subcloned and modified by AflII digestion and blunt end ligation to remove the intron provided in pCI. The virus was rescued after transfection of CSL503 cells as described previously (Vrati et al., 1996b) except that cationic lipids were used (Cameron et al., 1999) in place of lipofectamine. The virus proved difficult to rescue and several attempts were made. On the third attempt a cytopathic effect developed and medium from the cells was transferred to fresh permissive CSL503 cells to grow a stock of the virus (OAdV217A). The virus was subsequently passaged to expand the stock. Viral DNA was extracted from a portion of each passage, digested with BamHI and analysed by agarose gel electrophoresis. Passage 1 virus had a similar amount of the 3.1 kb band that was diagnostic for the cassette compared to the starting plasmid from which the virus was rescued. However, by passage three this band was significantly depleted relative to the band immediately above it and a smaller product of ~1.7 kb had appeared, demonstrating the instability of this particular genome. PCR amplification across the site of the inserted cassette and nucleotide sequencing revealed that a variety of deletion events had resulted in the loss of all or part of the HCMV promoter and the GFP coding and polyadenylation sequence.

Example 15

Construction and Stability of OAdV Carrying an HCMV Alkaline Phosphatase Cassette

Two plasmids, pOAdV216 and pOAdV616, were constructed in which a cassette containing the HCMV promoter and human placental alkaline phosphatase sequences was inserted in site I or site III of the genome, respectively (see FIG. **13**). The corresponding viruses were rescued and passaged in CSL503 cells. From gel electrophoresis it was apparent that the 1.95 and 1.8 kb bands representing the cassette in OAdV216 were lost rapidly after passage and by passage two had been replaced by a ~1.4 kb band. For OAdV616 however, the genome is stable. The diagnostic 1.8 kb band was retained, even after four passages.

Example 16

Construction and Stability of an OAdV Carrying Cassettes for Prostate Cancer Gene Therapy

A series of plasmids was constructed in which different promoters were linked to the purine nucleoside phosphorylase gene from *E. coli* and the polyadenylation signal of bovine growth hormone. The plasmids pOAdV220 and 222 contained the promoter from Rous sarcoma virus and HCMV, respectively. Plasmids pOAdV223 and 623 contained a prostate-specific promoter/enhancer element derived from the prostate-specific membrane antigene gene linked to the promoter the rat probasin gene promoter. These cassettes were inserted in the left to right orientation into the ApaI/NotI sites of pOAdV200 (site I) and pOAdV600 (site III), respectively. The corresponding virus from each of the above plasmids was rescued and passaged three times in CSL503 cells. DNA from each virus was analysed by Southern hybridisation using a radio-labelled 1.1 kb AgeI fragment from pOAdV220 as a probe. This contained the 3' end of the RSV promoter, all of the PNP and BGH sequences and ~300 bp of 3' OAdV genome sequence. The expected bands representing each respective cassette and the 3' BamHI fragment were observed for wild-type OadV, OAdV220, 223 and 623. However, for OAdV222 which contained the HCMV cassette in site I, the expected band was reduced in intensity and an additional smaller band was seen, indicating genome instability. Thus, site III is the preferred site for insertion of foreign gene cassettes. As site III is located between recently defined transcription units (Khatri and Both, 1998) the insertion of a discrete transcription cassette may not interfere with other viral functions. With this precedent, it is anticipated that expression cassettes could also be inserted into the OAdV genome between the Left Hand End and IVa2 transcription units (see FIG. **13**).

It will be appreciated by persons skilled in the art that numerous variations and/or modifications may be made to the invention as shown in the specific embodiments without departing from the spirit or scope of the invention as broadly described. The present embodiments are, therefore, to be considered in all respects as illustrative and not restrictive.

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The invention claimed is:

1. A recombinant vector comprising an ovine adenovirus genome and a sequence encoding a heterologous polypeptide, wherein the sequence encoding the heterologous polypeptide is inserted between E4 and E3 transcription units of the ovine adenovirus genome, and wherein at least one enhancer element obtained from intron 3 of the PSM gene is operably linked to the sequence encoding the heterologous polypeptide.

2. A recombinant vector as claimed in claim **1**, wherein the sequence encoding the heterologous polypeptide is inserted between nucleotides 26,682 and the 5' end of the E4 promoter of the ovine adenovirus genome.

3. A recombinant vector as claimed in claim **1**, wherein the sequence encoding the heterologous polypeptide is inserted between nucleotides 26,682 and 26,555 of the ovine adenovirus genome.

4. A recombinant vector as claimed in claim **1**, wherein the sequence encoding the heterologous polypeptide is inserted between an Apa1 and Not1 site between the E4 and E3 transcription units of the ovine adenovirus genome.

5. A recombinant vector as claimed in claim **1**, wherein the vector comprises a heterologous promoter.

6. A recombinant vector as claimed in claim **5**, wherein the promoter is located upstream from and is operably linked to the sequence encoding the heterologous polypeptide.

7. A recombinant vector as claimed in claim **5**, wherein the vector comprises at least one regulatory element obtained from intron 3 of the PSM gene operably linked to the heterologous promoter.

8. The recombinant vector of claim **1** wherein the ovine adenovirus vector has increased stability.

9. A recombinant vector according to claim 1 in which the enhancer element comprises nucleotides 1-171 of SEQ ID NO: 1.

10. A recombinant vector according to claim 1 in which the enhancer element comprises nucleotides 1-332 of SEQ ID NO: 1.

11. A method for directing expression of a coding sequence in a cell, the method comprising introducing into the cell a recombinant vector according to any one of claims 1-4, 5 and 6.

12. A method of delivering a sequence encoding a heterologous polypeptide to a target cell, the method comprising transducing the cell with a recombinant vector according to any one of claims 1-4, 5 and 6.

13. A method of delivering a sequence encoding a heterologous polypeptide to an animal cell, the method comprising administering to an animal or a cultured animal cell a recombinant vector according to any one of claims 1-4, 5 and 6.

14. A method of gene transfer to human cells, the method comprising administering to the cells a recombinant vector according to any one of claims 1-4, 5 and 6 such that the vector infects at least one cell and the infected cell expresses the heterologous polypeptide.

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